VOL. 34 JUNE 1958 NO. 6

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

WILLIAM V. McDERMOTT, JR.

RICHARD B. STARK
and JANET C. STARK

MANAGEMENT OF ULCERATIVE COLITIS
Transcription of a Panel Meeting on Therapeutics

BURRILL B. CROHN
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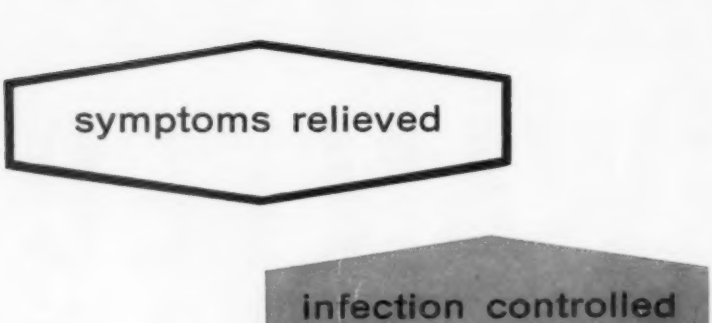

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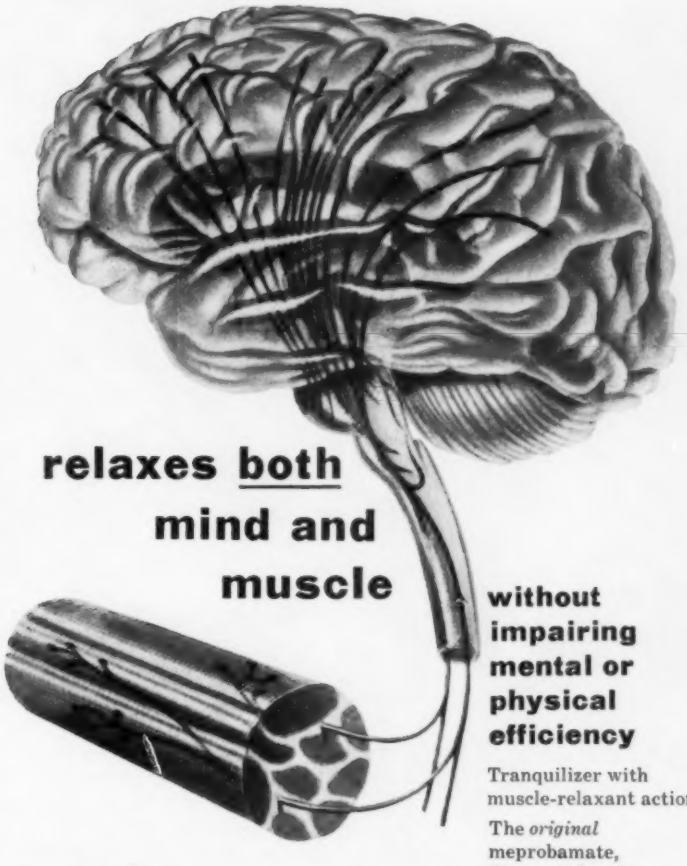

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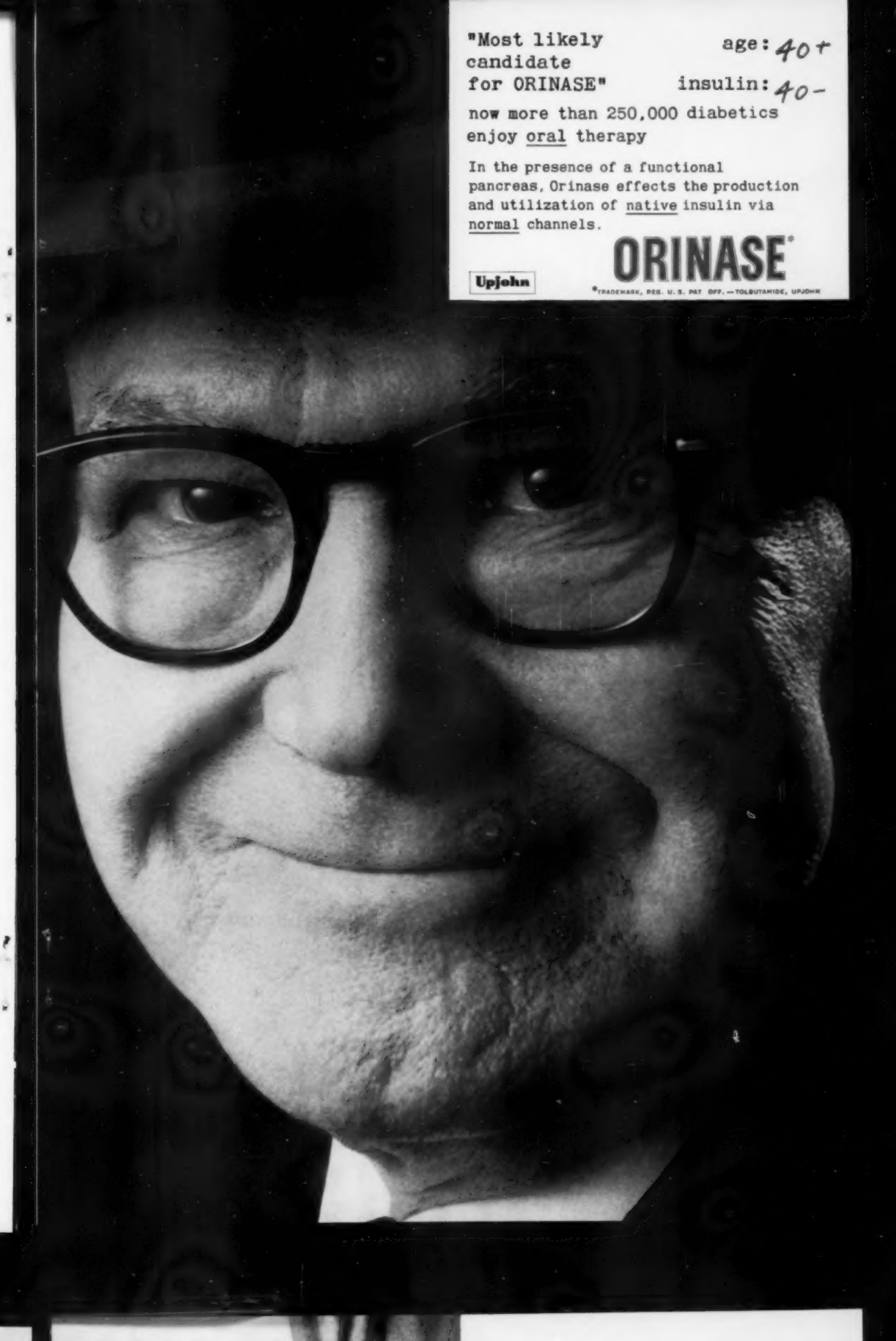
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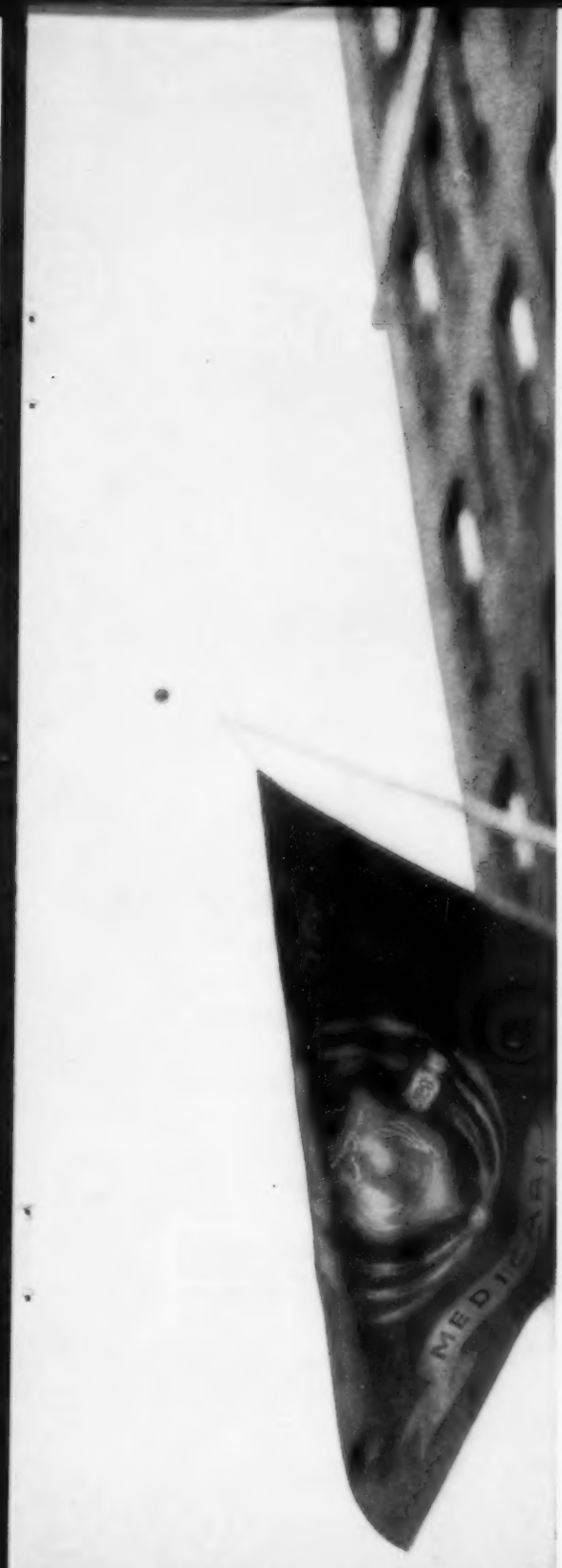

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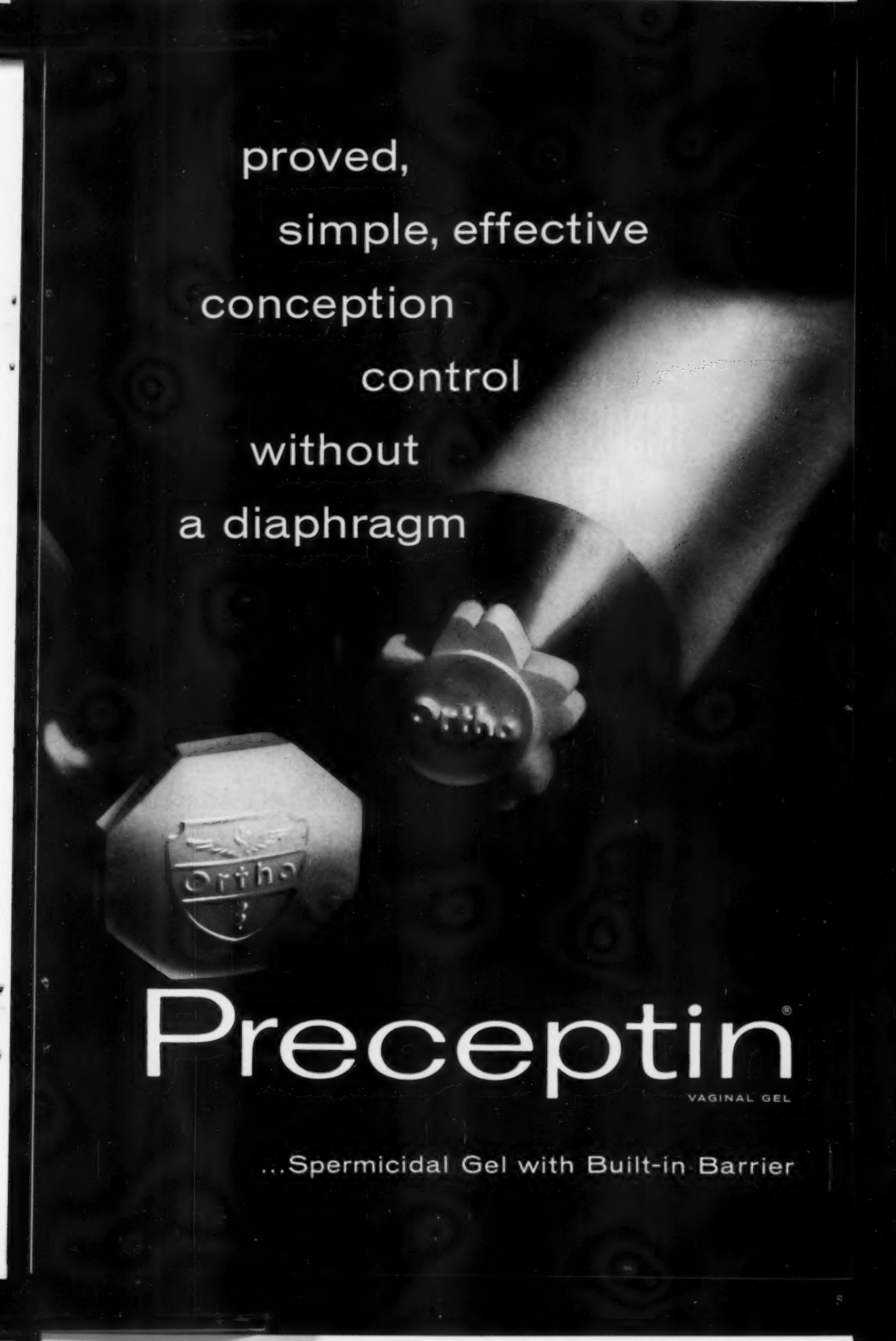
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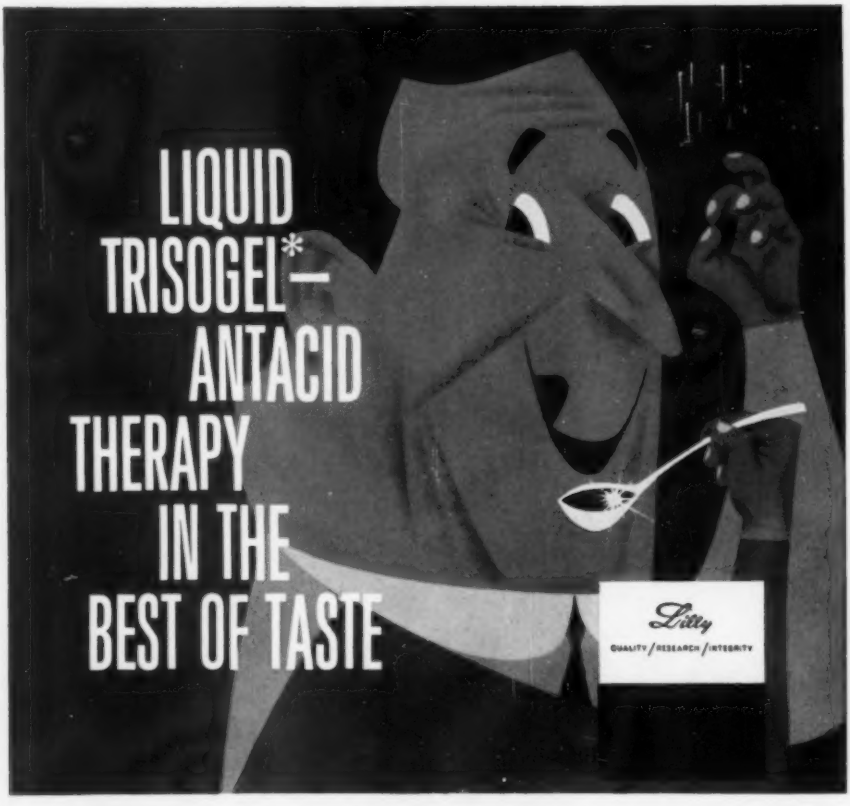

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $8.00. All other countries $9.00. Single copies 90c.
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BULLETIN OF
THE NEW YORK ACADEMY
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VOL. 34, NO. 6 JUNE 1958

THE ROLE OF AMMONIA INTOXICATION IN HEPATIC COMA*

WILLIAM V. MCDERMOTT, JR.

Assistant Clinical Professor of Surgery, Harvard Medical School; Assistant Surgeon, Massachusetts General Hospital.

HISTORICAL BACKGROUND

THE present interest in the relationship between ammonia metabolism and hepatic coma can be traced back to Nikolai Eck[1] who first demonstrated the feasibility of diverting the portal blood in a dog to the systemic circulation by constructing a fistula between the portal vein and the inferior vena cava; this fistula has since come to bear his name and it is common usage to use this term in reference to any surgically constructed shunt between the portal and systemic circulations. These original experiments of Eck which were carried out in 1877 were important primarily because they stimulated work in Pavlov's laboratory on the physiological effects of such a shunt. In 1893 Hahn and associates[2] observed a syndrome of neurological abnormalities in these dogs and on empirical grounds related it to a high intake of meat. Since that time this syndrome has come to be known as "meat intoxication".

* Presented at a combined meeting of the Sections on Medicine and Surgery with the Stated Meeting of The New York Academy of Medicine, April 4, 1957 as part of a Symposium on *Diseases of the Liver*. Manuscript received June 1957.
From the Department of Surgery, Harvard Medical School and the Surgical Services, Massachusetts General Hospital, Boston, Mass.
Supported by the National Institutes of Health, U. S. Public Health Service.

Over the ensuing years, considerable work was done in an attempt to clarify the etiology of this bizarre syndrome; the intoxication was variously ascribed to many substances of bacterial or chemical origin but in none of these studies was there any definitive proof of the etiological agent.

Shortly after these observations on the occurrence of meat intoxication in the Eck fistula dog, interest arose in the metabolism of ammonia stimulated by the work of Folin and Denis.[3] Nash and Benedict[4] showed that the kidneys, instead of excreting ammonia from the total body pool contributed to its formation and demonstrated that bilateral nephrectomy caused a rise in all the nitrogenous constituents of the blood except ammonia which remained normal until death. Prompted by these previous studies, Burchi,[5] in 1927, suggested that disturbances in ammonia metabolism might account for some of the symptoms of "hepatic coma". With the increasing knowledge of the mechanisms of urea synthesis in the liver, Van Caulaert and associates,[6, 7] Kirk[8] and Gaustad[9] all described central nervous system symptoms in patients with liver disease which, they suggested, might be attributable to ammonia by-passing the liver through portal-systemic shunts.

Because of the lack of a satisfactory technique for measurement of blood ammonia, no further progress was made in this field until Conway[10] published his studies on microdiffusion analysis and offered a satisfactory method of measuring peripheral blood ammonia.

Again, however, there was a considerable lag period before this basic technique was adopted for use in clinical medicine. In 1952 Stahl and his colleagues[11, 12] in France and workers in the Thorndike Memorial Laboratories in Boston,[13, 14] demonstrated that symptoms resembling hepatic coma could be induced in patients with cirrhosis of the liver by the administration of nitrogenous material by mouth. In 1953 studies from this laboratory were completed on a patient who had a resection of the portal vein for cancer of the pancreas with an end-to-side anastomosis constructed between the superior mesenteric vein and the inferior vena cava; this patient developed a series of reversible disturbances of central nervous system function which were found to be associated with the ingestion of protein or other nitrogenous substances, were associated with a striking rise in the peripheral blood ammonia and which could be controlled by limiting the nitrogenous intake and by the administration of antibiotics by mouth.[15]

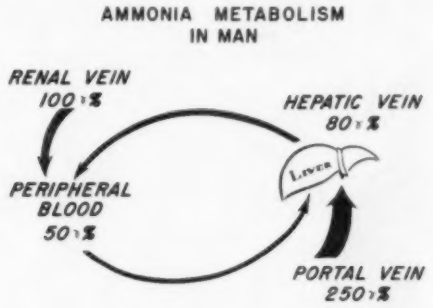

Figure 1*—A simplified diagram of ammonia metabolism in man. Published in *Annals of Surgery*, Oct. 1954 (ref. 18).

* Figures 1-4, inclusive, reprinted by permission.

Since that time there has been an increasing number of studies on this phenomenon of central nervous system symptoms associated with disease of the liver or portal circulation and, while the intricacies of ammonia metabolism in man are far from clarified, there would appear to be a very distinct relationship between the phenomenon of absorbed ammonia from the intestinal tract by-passing the liver and the occurrence of central nervous system symptoms.

The Effect of Gastrointestinal Hemorrhage in the Presence of Portal Hypertension

Figure 1 is a simplified diagram of ammonia metabolism in man based on information obtained in this hospital over the past few years. This demonstrates how spontaneously developed or surgically constructed portal-systemic shunts may lead to hyperammoniemia. It should be stressed at this time that existence of an elevated blood ammonia level is, in the main, an index of collateral circulation around the liver and not specifically a test of liver function. It is probable that an advanced degree of liver damage could so impair the normal mechanisms of urea synthesis that ammonia would accumulate and rise to abnormal levels in the blood; from observations to date however, this would appear to be a more unusual event than the hyperammoniemia associated with extensive portal systemic collaterals and an excessive nitrogen load in the intestinal tract.

This brings us to a consideration of the effect of blood in the gastro-

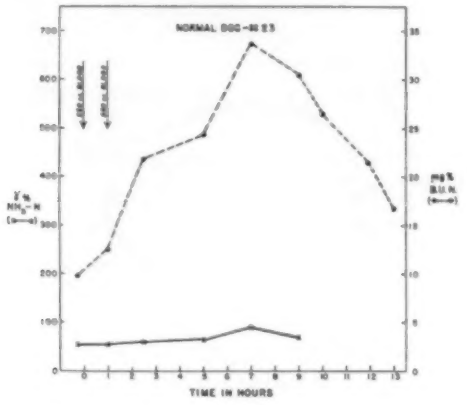

Figure 2—Effect of blood in the gastrointestinal tract of a normal dog. Published in *Annals of Surgery*, Sept. 1956 (ref. 17).

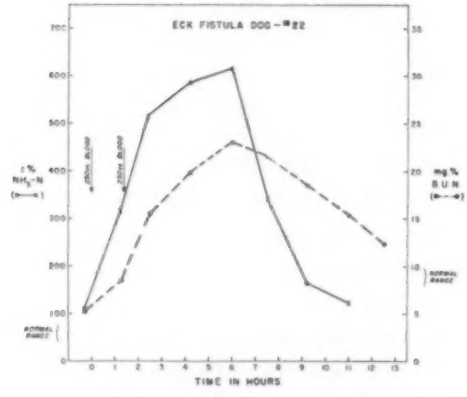

Figure 3—Effect of blood in the gastrointestinal tract of a dog with an Eck fistula. Published in *Annals of Surgery*, Sept. 1956 (ref. 17).

intestinal tract in the normal dog and in the dog with a surgically constructed Eck fistula. In Figure 2 we see the effect of the administration of blood to a dog via an inlying gastric tube. There is a distinct rise in the blood urea nitrogen, a syndrome which has been referred to as "alimentary azotemia" but the blood ammonia levels stay within the

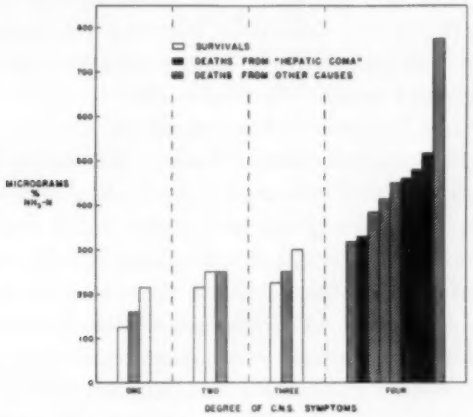

Figure 4—Effect of hemorrhage from esophageal varices on ammonia levels and clinical status. Published in *Annals of Surgery*, Sept. 1956 (ref. 17).

normal range. In the dog with an Eck fistula however, Figure 3, a striking hyperammoniemia develops and symptoms can be induced which resemble the symptoms of meat intoxication in the Eck fistula dog, a phenomenon which studies in this laboratory[16] have suggested was due to ammonia intoxication.

This experimental study bears such a striking resemblance to the situation which exists in a patient who enters the hospital with bleeding esophageal varices that a comparison is inevitable. Obviously, the existence of esophageal varices presupposes some type of portal bed block and the development of collateral circulation between an obstructed portal outflow and the systemic circulation. With these facts in mind, a series of patients with bleeding esophageal varices were studied with particular emphasis on disorders of ammonia metabolism.[17] In Figure 4 we see the correlation between blood ammonia levels in patients with acutely bleeding esophageal varices and the degree of disorder of the central nervous system. It should be stressed at this point that these symptoms are not related to "shock" or to any consistent degree of derangement of liver function. In other words this is primarily an absorptive phenomenon. If this phenomenon of "ammonia intoxication" exists as a clinical entity, where and how does this hyperammoniemia exert its untoward effect? It has been suggested[18, 19] that ammonia may

combine with alpha keto-glutarate and thus interrupt the citric acid cycle; in turn this would effectively interrupt the normal pathways of aerobic glycolysis on which the central nervous system depends so much for its normal metabolic activity. Proof of this hypothesis is extremely difficult to obtain and much of the evidence in favor of this thesis depends upon indirect evidence. We know that "hepatic coma" is almost invariably associated with elevations of the blood pyruvate and lactate,[20] that glutamine[21] is elevated in the cerebrospinal fluid and that cerebral oxygenation is decreased in patients with hepatic coma.[22] Weil-Malherbe[23] has reviewed the evidence which pointed towards an important role of L-glutamic acid in the maintenance of normal central nervous system physiology because of its ammonia binding capacity. With this in mind and because of the known importance of glutamic acid in carbohydrate metabolism, Walshe[24] suggested the use of glutamic acid in the treatment of "hepatic coma" and reported good results in five episodes occurring in three patients. The value of glutamic acid as a clinical tool has been the subject of controversy in the subsequent years; it is apparent that glutamic acid is no panacea in the treatment of this severe metabolic derangement nor should it be expected that the administration of one amino acid could effectively restore all patients with multiple gross derangements of metabolism to a normal status. Nonetheless, it is apparent that glutamic acid does have an ammonia binding capacity in man,[25, 26] and that it undoubtedly is a useful adjunct in the treatment of patients with "ammonia intoxication".

Another amino acid has more recently come to prominence in relation to this metabolic derangement. Greenstein and associates[27] reported that administration of arginine protected rats from ammonia intoxication induced by the administration of large amounts of other amino acids. These experimental observations were tested clinically by Najarian and Harper[28] and have since been utilized in other centers[29, 30]. Again, it would appear that arginine has a very definite effect on hyperammoniemia and probably contributes to the correction of at least one of the abnormalities associated with "hepatic coma". Again, however, it should not be expected that this will prove to be a universal panacea nor should it be expected that any one administered substance could effectively reverse all the derangements associated with abnormalities of the liver and portal circulation.

Conclusion

At the present time we cannot give a single answer to the complex biochemical changes associated with the clinical syndrome of "hepatic coma". In its simplest manifestation this syndrome appears in a patient with a well compensated or normal liver who has spontaneously developed or surgically constructed shunts between the portal and systemic circulations, and has a nitrogenous load introduced into the gastrointestinal tract. This particular set of circumstances probably represents ammonia intoxication since it is not dependent on severe liver damage and the syndrome should be reversible. We can at least outline a logical course of therapy based on the information that is available.

This plan of therapy can be summarized as follows:

1. Withdraw "nitrogen" or in the case with a patient with bleeding esophageal varices, make an early and vigorous effort to control the bleeding.

2. Immediate use of cathartics and enemas to eliminate the pool of nitrogenous material in the gastrointestinal tract.

3. Oral administration of broad-spectrum antibiotics in order to eliminate as much as possible the bacterial flora of the intestinal tract which are the source of the enzymes which form ammonia from ingested "nitrogen".

4. Parenteral administration of glutamic acid because of its known ammonia binding capacity.

5. The administration of arginine because of its apparent effect in lowering the blood ammonia and increasing the blood urea nitrogen.

As stated above it would appear that there is a specific syndrome of ammonia intoxication with a consistent biochemical and clinical pattern. This however, refers primarily to the syndrome which we have described as "exogenous hepatic coma". In the patients with "spontaneous hepatic coma" in whom no specific precipitating nitrogenous factor can be incriminated and in whom there is extensive liver damage, the pattern of the disordered ammonia metabolism as reflected in the peripheral venous blood is far from consistent and is not related in degree to the depth of the "coma". This inconsistency has been recognized by many investigators and a number of possible explanations have been offered. Studies on arterial venous differences in ammonia levels, and on the cerebral and peripheral uptake in release of ammonia[31, 32] have

been extremely interesting and contributed to our understanding of the puzzling patterns which occur in the presence of decompensating liver function. A recent very intriguing concept has been offered by Jacquez and by Lawrence and their associates[33, 34] working in Randall's laboratory. These investigators have pointed out the importance of acid-base balance and have utilized the concept of pNH_3 in the transport of ammonia across the cell membrane. We do not as yet know exactly what we are measuring when we refer to the total "ammonia" content of blood as either measured by Conway[10] or Seligson[35] techniques. We are faced with the difficulties of interpreting what is going on in the cell from measurements of circulating blood; we do not understand the factors controlling the transport of ammonia across the cell membrane; we have no satisfactory tools as yet for measuring the normal intracellular mechanisms of protection against abnormal concentrations of ammonia nor have we anything but indirect evidence to point out how ammonia can be toxic to the cell.

Perhaps it might be well to close at this point with a quotation from Thurber's "Fables For Our Times",—"it is better to know some of the questions than all of the answers".

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MANAGEMENT OF ULCERATIVE COLITIS

*Transcription of a Panel Meeting on Therapeutics**

BURRILL B. CROHN . . . Moderator

Consulting Gastroenterologist, The Mount Sinai Hospital; Formerly, Associate in Medicine, College of Physicians and Surgeons, Columbia University

Panel Members

GEORGE L. ENGEL

Associate Professor, Departments of Medicine and Psychiatry, University of Rochester School of Medicine and Dentistry, Rochester, New York; Associate Attending Psychiatrist and Associate Attending Physician, Strong Memorial Hospital, Rochester, New York

CHARLES A. FLOOD

Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Attending Physician, The Presbyterian Hospital

JOHN H. GARLOCK

Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon, The Mount Sinai Hospital

* Presented at the Monthly Panel Meeting on Therapeutics (Fifth Series) at The New York Academy of Medicine.

MODERATOR BURRILL B. CROHN: The topic assigned to us today is the *Management of Ulcerative Colitis.*

The incidence of ulcerative colitis has increased tremendously during recent years, or at least the recognition of the disease has increased. I remember when as an intern at The Mount Sinai Hospital 50 years ago a case of ulcerative colitis was rare and was regarded as something most unusual. At that time, you will recall, the sigmoidoscope was a long instrument which had no electric light; a nurse held a candle or lamp and the examiner used a head mirror. No radiography was available so that the recognition of the disease was most difficult, if it did occur with the frequency with which it occurs today. Today the hospitals are full and many beds are occupied by patients with ulcerative colitis. With the apparently greatly increased number of patients with this condition, the problems of treatment and management have increased progressively over the years.

I shall first ask Dr. Flood to discuss the medical aspects of the management of ulcerative colitis.

DR. CHARLES A. FLOOD: Since this is a discussion mainly of the management of this disease, little need be said concerning etiology or diagnosis except to state that its etiology is still unknown; that many theories have been suggested, and although there is a certain amount of evidence to support a number of them, I think the majority of those especially interested in ulcerative colitis still regard it as a disease of unknown etiology and, therefore, particularly difficult to manage medically.

The diagnosis of ulcerative colitis is relatively simple. The clinical picture is usually sufficient to suggest the presence of this disease. The anatomical changes which accompany it can be visualized on proctoscopic examination and on x-ray. Of these two methods of examination, the proctoscopic examination is apt to be more revealing in most cases. About 90 per cent of patients with ulcerative colitis have visible changes in the rectum and rectosigmoid. The x-ray examination may reveal nothing or it may reveal changes which might suggest the possibility of ulcerative colitis but still be compatible with a normal colon, or the changes disclosed by x-ray may be typically those of this disease.

In the management of patients with ulcerative colitis it is important to attempt to classify the disease in terms of its extent and its severity. There is a wide range of severity in this disease, all the way from the

case of mild proctitis to the severely ill patient.

In mild proctitis, which most people believe is a manifestation of ulcerative colitis, the patient has few symptoms, the diarrhea is mild, there may be a little blood in the stool. Proctoscopy reveals inflammatory changes and x-ray examination is essentially negative. In such a situation the disease runs a mild course. The patient will improve under expectant treatment of any type, is apt to go into early symptomatic remission, only to exhibit a recurrence of symptoms at some future date. In those patients whose disease is initially limited to proctitis, the disease seldom seems to extend up the colon to any extent. Their medical management seems to be relatively simple.

At the other extreme is the patient with a fulminating picture of ulcerative colitis, the severely ill individual with fever and other constitutional symptoms, generally with a total involvement of the colon, although this picture may also be present in patients who on x-ray appear to have only partial involvement of the colon. In many respects these patients present a particularly difficult problem in management. They are often so seriously ill that the question of the necessity for early surgery arises. They present problems in the maintenance of fluid and electrolyte balance. They often are malnourished. They often present serious neuropsychiatric problems, and this is one of the most difficult forms of the disease to manage.

Between these two extremes of the severely ill patient and the patient with proctitis are found the majority of patients with ulcerative colitis who have involvement of the rectum and of the colon with symptoms of varying degrees of severity.

As a general rule, treatment in the management of this disease is largely supportive in terms of diet, sedation, vitamin therapy, the use of antibiotics or sulfonamide drugs, the use of transfusions and other supportive measures. The majority of patients on such a regimen will go into symptomatic remission. A certain number of patients will require the use of other modes of therapy, and in recent years the steroids have become available for treatment, particularly of the sicker patients.

We have recently been interested in reviewing our results of management of these different types of ulcerative colitis in the clinic at the Presbyterian Hospital, and with your permission, I would like to summarize very briefly the long term results as we have seen them.

Only a few patients have gone into complete remission and remained in remission over a period of years. Approximately 95 per cent of our patients with chronic ulcerative colitis, even though they have periods of remission have, as they have been followed over the years, had a recurrence of symptoms at some later date. As mentioned earlier, the best outlook is in the patients with proctitis. These patients are seldom incapacitated by their symptoms and are easy to manage. The patients with fulminating disease have had a very disappointing course on medical treatment. For example, in a group of some 20 patients who ran a high and continuous fever for over two weeks, only four of the 20 remain under medical treatment. The others were either operated on early or later in the course of the disease, or have died. The results in the fulminating picture have been sufficiently disappointing to lead us to believe that early surgery should be seriously considered more often in these circumstances.

The problem of the patient with less severe symptoms but with incapacitating symptoms which last for long periods of time is also difficult to manage. The patient who has continuing diarrhea, with six to ten stools a day for a period of several months, who does not respond to simple supportive treatment, often becomes very discouraged, often seeks help elsewhere, presents a problem as to whether we should continue with medical treatment, or whether we should have recourse to surgery. In this group it is very difficult to set down any rules of action. The patients who have less severe symptoms, however, under current conditions may do extremely well under steroid therapy.

In our own experience we have largely limited the use of steroids to those patients who have failed to respond to other simpler measures. In using steroids for the sicker patients under these conditions, it has been our experience that approximately half of these patients do respond in terms of disappearance of constitutional symptoms, control of the diarrhea, increased sense of well being and improved nutrition. As patients have been followed over a period of time under steroid therapy, or subsequent to it, we have not been able to convince ourselves that the use of steroids has modified the long term course of the disease. This is a problem for which I believe there is no clearcut solution at the present time. Our impression is that steroid therapy used in ulcerative colitis is purely suppressive, suppressing the inflammatory response and eliminating in large degree the symptoms without

modifying the underlying process. Therefore, it remains to be seen how useful steroid therapy will be in the long term management of the patient, although it is clear that it is of great value in the immediate relief of the severely ill. The use of steroids has, in some instances, been accompanied by unfavorable results, both the undesirable complications which arise in the use of steroids for any disease and those complications and problems which are peculiar to ulcerative colitis. We have had a few patients who developed brisk bleeding and perforation when these drugs were used. When the patient is on steroid therapy it may be extremely difficult to determine his exact clinical status, and perforation may occur and not be recognized.

We have also had difficulty in certain instances with patients with severe ulcerative colitis who, after a very brief period of observation, had been placed on steroid therapy and have had symptomatic remission to some degree, but who subsequently do not continue to improve, and the question then arises as to whether surgical therapy should be recommended. At times it is extremely difficult to evaluate the severity of the disease in patients who are under steroid therapy. In some instances it may be advisable, with seriously ill patients, to withhold steroid therapy for a sufficient period of time to establish whether or not the clinical picture already warrants surgical intervention.

The present status, then, of this problem is that the majority of patients will have symptomatic remission under treatment with available medical measures. We have subjected approximately 20 per cent of our patients to surgery. I believe the incidence varies in different clinics, but this is probably an average figure at the present time. In the future we hope we shall learn to select better those patients for whom surgery is indicated and for whom medical treatment should be interrupted earlier than it has been in the past.

MODERATOR CROHN: Thank you, Dr. Flood. If our audience does not ask you questions, I shall do so!—particularly regarding some points in your use of the steroids.

I shall next call upon Dr. George Engel. I am responsible for bringing Dr. Engel from Rochester, N. Y., to present the psychosomatic aspects of ulcerative colitis. I brought him down to learn his views. I suspect he thinks I need a lesson! Dr. Engel!

DR. GEORGE L. ENGEL: Before presenting my remarks I would like to make one identifying point about myself, namely, that while I have

been interested in the psychological aspects of patients with ulcerative colitis, I have seen those patients as an internist with psychological training. I think this is of some importance in respect to my points of view because I have taken full care of many of these patients while with others I have worked with another internist or with a surgeon. Hence my roles have ranged from the physician to the psychotherapist.

I would also like to clear the air on another point. What I shall have to say about the psychological aspects of treatment of ulcerative colitis is not in any way to be interpreted as placing something called psychotherapy in opposition to other techniques of treatment which are directed toward different aspects of the care of the patient. Accordingly, many of the things that Dr. Flood has spoken of also fall in the area of our treatment program, and I am sure that many of the things that Dr. Garlock will have to say will also fall in the same area. Now, since our time is extremely limited, I will make some dogmatic statements which you are welcome to challenge afterwards.

My first dogmatic statement is that, so far, there is no known technique for the cure of ulcerative colitis, be it medical, surgical, or psychological. The closest approach to a known cure for ulcerative colitis is the surgical approach, namely, ileostomy and total colectomy; but in my experience a significant number of patients so treated remain vulnerable to the development of an ulcerative ileitis, (to be distinguished from the regional ileitis to which Dr. Crohn's name is attached).

The second simplified and dogmatic statement applies to the setting in which the disease becomes manifest. We have been interested to learn as much as we possibly can of the conditions, the circumstances, the settings, and the factors which may play a role in determining when a patient falls ill and how and when a patient recovers. In these observations we have been impressed that one phenomenon seems to appear over and over again. We regard it not as a primary etiologic factor but rather as a condition, perhaps necessary but not a sufficient condition for the genesis of the process in the colon that we call ulcerative colitis. It is that these patients are characterized by an unusual vulnerability to the loss of loved or invested persons. Let me try to phrase that in a broader sense: All people have relationships with other people, their families, friends, as well as jobs, work, etc., etc. All people respond to loss or threats of loss of loved persons, of job, prestige, of position, etc., with a variety of reactions, the most normal of which is grief.

Those patients who are vulnerable to ulcerative colitis—note that I say vulnerable to ulcerative colitis because this infers there is some underlying pre-existing condition which must exist—seem to be peculiarly sensitive to such losses and to be inclined to develop the condition known as ulcerative colitis in relationship to such losses. I have to be somewhat more precise than that because our more microscopic examination of the circumstances and the responses reveals that it is when the patient who experiences a real, threatened or phantasied loss reacts with a mood or an affect state which could be characterized by helplessness, hopelessness, or "this is too much, I can't go on," or "it is too much for me, I don't know what to do," that the distinctive mucosal —submucosal reaction of the bowel which we call ulcerative colitis develops. This may occur within a matter of hours or days.

Conversely when these patients are successful in overcoming such a reaction to loss, they may very well overcome the attack of ulcerative colitis, provided the damage to the bowel has not progressed to the point where regeneration and recovery are no longer possible. Also, if these patients experience a loss, real, threatened or phantasied, but do not become hopeless or despairing, they will often develop some other symptom or illness, but not ulcerative colitis. The most common alternative symptom is headache. I should emphasize that the affect state just described is not necessarily conscious or acknowledged by the patient.

This may seem to you like a highly abstract, theoretical, and impractical point, yet from my experience this proves to be the crucial point in the treatment of patients with ulcerative colitis regardless of the technique used, because it develops that the person with whom the patient establishes the relationship which compensates to some degree for the real, threatened or phantasied loss is usually the doctor. The doctor thus becomes a person of great help or threat to his patient because the doctor who is ignorant of this fact may unwittingly help this patient tremendously by being a good doctor, taking good care of the patient's medical and other related problems, but he may also unwittingly harm his patient by not recognizing the patient's dependence on him. He may fail to appreciate the significance to the patient of his leaving town, failing to see his patient, breaking an appointment, or in other ways leaving the patient in the situation of not feeling taken care of. I emphasize that this principle operates regardless of what

other measures are used.

In discussing medical treatment, Dr. Flood repeatedly used the words "supportive treatment". In my experience, the effectiveness of this supportive treatment is very closely linked to the relationship with the physician. I have repeatedly seen drugs and techniques of treatment which were effective the first time, fail the second time simply because the patient invested the drug with the power of the physician. When he relapses, this element is now missing.

In respect to surgical treatment, I have been impressed that patients who come to surgery without a satisfactory relationship with their physician, be it the medical man or the surgeon, do poorly. In our own series of 40 patients, of the 9 patients who died, 8 were patients who did not establish relationship with any physician in the hospital. The ninth patient had a lengthy psychotherapeutic relationship with me yet died two weeks post total colectomy and ileostomy with a fulminating, ulcerative ileitis when all three of her physicians, her surgeon, internist, and myself, simultaneously went out of town to meetings. From this tragic experience I learned the importance of being on hand when my patient is required to undergo an operative procedure.

I would close, then, with this general statement, which I presume there will be opportunity to elaborate on later: Regardless of the technique of treatment that one embarks on, be it medical, surgical, or psychological, all the aspects of the disease must be kept in mind, all aspects of the process that is going on. The physician who takes care of the patient with ulcerative colitis should assume that he is undertaking the care of this patient indefinitely. By this I don't mean that he has to continue to see him at frequent intervals, but rather that the patient should continue to regard him as his physician even after long and successful psychotherapy. In those instances in which there is irreversible change in the bowel, where over a period of months there is continued diarrhea, or bleeding, or where radiological evidence shows extensive changes in the bowel wall, or where there is development of abscesses, fistulous tracts, etc., it would be my judgment now that the primary task of the psychotherapist, whether this psychotherapist be a psychiatrist or whether he be the internist who is dealing with this patient with psychotherapeutic insight, should be to prepare the patient for surgery bearing in mind that the optimum time for surgery is

going to be that time at which the patient has achieved his strongest relationship with the physician.

There are also certain contra-indications to surgery, which I presume Dr. Garlock will talk about. An obvious one is in the patient with disease of the ileum. What I have to say would not apply in the same degree to the patient whose disease is restricted to a very small portion of the bowel, where it is possible to temporize much longer. The main point that I want to emphasize is that the relationship to the physician is the most important tool we have in the treatment of ulcerative colitis.

MODERATER CROHN: Thank you, Dr. Engel. That is a very enlightening statement of the relationship of ulcerative colitis to psychosomatic factors and of the role of psychotherapy in the management of disease. I think by this time every physician who treats ulcerative colitis knows that if he is not in complete emotional rapport with his patient, if the patient has not a fondness for him, if the physician does not like the patient, if there is no empathy between them, the physician is doomed to fail. Our successes occur when we have a willing and admiring patient.

In Dr. Engel's presentation I missed the question of the role and relationship of the mother to the patient, which is so commonly present in cases of ulcerative colitis, and which is so well represented in this disease.

With our best efforts we fail in a fairly large percentage of cases. We do the best we can but all too frequently we eventually have to call upon the surgeon to effect a complete radical cure of a disease which otherwise would often be regarded as relatively incurable.

Dr. Garlock, will you present the surgical aspects of this problem, including both the surgical successes and failures in the management of this disease.

DR. JOHN H. GARLOCK: In any disease, the cause of which is completely unkown, all forms of therapy are essentially empiric, whether it be supportive therapy, psychotherapy, or surgical therapy. However, I would like to emphasize that one must constantly keep in mind the pathological process that is going on in the bowel, since it is upon this basis that surgical therapy is considered.

I have said that the therapy is empiric, which reminds me of an excellent example of what I mean. It seems worth while to repeat the story here. It concerns a boy on the wards in our hospital who was

acutely ill with fulminating ulcerative colitis. The incident occurred about eight or ten years ago, when he was on the medical service. Every form of therapy had been employed. There were no steroids available at that time, of course. We were about to be called in to do an emergency ileostomy when the assistant resident approached his resident and said, "That boy in the back of the ward with acute ulcerative colitis would like to have a bologna sandwich. Have you any objection if I go down and buy him one?" and the resident said, "Well, we have tried everything else, we might try that," and he did. Curiously enough this patient went on to a remission within 48 hours. Now that is empiric therapy! I am quite sure that the bologna sandwich had nothing to do with his remission. I am also quite sure Dr. Engel will say that there was a definite relationship established between him and the assistant resident. That may have been a factor.

Now we have gone through a period of trial and error during the last 20 years to determine the rationale and indications for surgical therapy. Our experience at Mount Sinai Hospital has been the same as Dr. Flood's with respect to the incidence of surgical therapy in the total group. Approximately 22 per cent of the ulcerative colitis admissions to the hospital require surgical therapy. We have tried to make the treatment of ulcerative colitis a group problem in which the gastroenterologist, the internist, the psychiatrist, the surgeon, the social service department, and the nursing staff are all parts of a team, and we try to determine by reviewing these patients daily which ones will require surgical treatment. Over the years we have gradually arrived at certain criteria which I should like to present to you today.

In the first place, we believe that surgery is indicated when extensive irreversible pathological changes have taken place in the bowel, colon and rectum, which can be determined by sigmoidoscopic examination, the clinical course of the patient, and the barium enema.

In the second place, there is a definite indication for surgery to save life in the acute fulminating variety of this disease. I consider this variety the most difficult of all to treat from the standpoint of trying to determine whether surgery is indicated at all. It must be emphasized that, characteristically, ulcerative colitis of the acute variety for some unknown reason may abort abruptly with complete defeverescence of symptoms and resultant apparent complete clinical remission which may last for years. More often than not, surgery will be definitely

indicated in order to save life.

Third, we believe that the devolpment of polypi, inflammatory polypi, in the colon in the course of chronic ulcerative colitis must be considered a positive indication for surgery because it is fairly well agreed throughout the country that the incidence of carcinoma, secondary to polypi on the basis of an ulcerative colitis, is fairly high.

Fourth, we think that surgical treatment is indicated for the pathological complications of the disease. We classify these as, (a) pericolonic abscess due to slow perforation of an ulcer, usually in the left colon, the formation of pericolonic abscess which is incised and drained and followed by a persistent fecal fistula. This indicates irreversible change in the bowel, and can only be cured by removing the offending organ; (b) the presence of extensive perianal fistulae or rectovaginal fistulae in the female, is considered a positive indication for surgery in order to effect a cure; (c) is the not infrequent complication of acute exsanguinating hemorrhage from the diseased colon which frequently calls for emergency surgery to save life; and (d) the complication of impending perforation or acute perforation is a positive indication for surgical intervention.

I think that covers the surgical therapy. We will go into some of the details later, I hope.

MODERATOR CROHN: Very good, Dr. Garlock.

May I have some questions from the audience? If not, I shall have to heckle these speakers myself, and I would like to have some assistance from you. I have one question, directed to Dr. Engel: In the employment of psychotherapy as an adjunctive treatment, should the gastroenterologist or the internist, or the general practitioner do this or should the patient be referred to a specialist in psychotherapy?

DR. ENGEL: That is an extraordinarily difficult question to answer. It depends a good deal on where you are practicing and who is available. I think one of the greatest problems is the availability of trained people. It should be implicit in what I said that a particular awareness on the part of the physician of the significance of his relationship to the patient is in itself an important if not essential psychotherapeutic measure in the care of the patient.

It is very difficult for me to prescribe what kind of an attitude or how you should behave toward your patient, yet I think your criterion should be based on knowing the significance to the patient of these

kinds of losses or threatened losses, including the loss of the doctor. For instance, I never leave town without letting my ulcerative colitis patients know where I am, and how I can be reached; but I am very infrequently called. It is the knowledge that I *can* be called that is important, the knowledge that they know where they can reach me. But it is catastrophic if the patient calls me up and learns that I am not accessible. I have had patients who have carried a prescription in their purses, this being the only means of sustaining a contact. Recently I had a patient whom I had not seen for a year who moved to a new house only to discover that the telephone company had not yet installed any cables in that neighborhood, and the telephone could not be installed in their home for an indefinite period of time. The patient wrote me a letter, which I interpreted to be a warning that trouble was ahead unless easy access to me was quickly reestablished. I called the telephone company and on the basis of a medical need,—that the patient might bleed,—arranged with them to have a temporary line put in. That evening the patient's husband called me to say that his wife was having a relapse. I gave him the information that I had already requested the telephone company to put in a line and had been assured that it would be installed in a couple of days. I prescribed some Demerol, and within 24 hours the attack had subsided. The point here is that the maintenance of the contact was the psychotherapeutic maneuver. This kind of psychotherapy should be within the province of any good physician, and many good physicians do this without knowing the special significance of what they are doing.

When it comes to a more intensive type of psychotherapy involving reorganization of personality structure, then I think one has to have some kind of training. I think there are some internists who have that kind of training, and we are training such internists in Rochester. By and large, internists do not have this kind of training. If a psychiatrist is to do this, it should be a psychiatrist who has a very good understanding of the dangerous situation that he is dealing with because ulcerative colitis is a dangerous disease. Things can happen very quickly and disastrously.

MODERATOR CROHN: *I think part of that question was: Would you call in a psychiatrist in the presence of an acute fulminating febrile ulcerative colitis?*

DR. ENGEL: I doubt it. Again, I would have to know whom I was

calling in. When I am called in in such a situation, which happens not infrequently, I find that I have to function first as an internist. The patient is too sick to deal with psychological content, and I will not accept such a referral, whether it come from the medical man or the surgeon, without his understanding that in order for me to be of use I must be able to leave orders, to change orders, and to participate actively in the medical care of this patient. Otherwise there is little or no hope that a relationship can be established. In Rochester I think a number of physicians have come to recognize that you can't be all things to all people, that there are some patients that you, as an individual, can't relate to, and if so, you should get help from someone else who can relate. Neither I, nor anybody else, can relate to all patients.

MODERATOR CROHN: I asked that question because the patient is often so sick that he can't raise his head. I have had unfortunate experiences in asking a psychiatrist to achieve a therapeutic result in a prostrated patient with a temperature of 103° F.

We have so many questions that we will have to be brief in our answers! Dr. Garlock: At what age, if at all, would you consider a total colectomy in youngsters of 8 to 13 years of age who have ulcerative colitis? Do you operate on that type of patient?

DR. GARLOCK: That is a "spiked" question!

MODERATOR CROHN: It *is* a "spiked" question because we have at the moment a 10½ year old girl whom Dr. Garlock and I are jointly treating. She is so sick that I have urged colectomy and ileostomy but Dr. Garlock is holding out day after day.

DR. GARLOCK: It seems like a strange situation where the surgeon refuses to operate and the gastroenterologist insists on it. That is exactly the case in this instance. It is well known, at least it is so in my experience and in the experience of those, like Dr. Robert Gross in Boston, who see many sick children, that these children under the age of 10 to 12 years, do very poorly when operated upon for acute fulminating ulcerative colitis. The mortality is high. They don't respond to the ileostomy as quickly as adults do. The outlook is pretty bad. On the other hand, there is a high incidence of spontaneous recovery in children. I have been loath to operate on children for acute ulcerative colitis, and it is for these reasons that I have deferred operating on the little girl in question. Very often one uses clinical hunches when treating sick patients, and it has been my hunch—perhaps it is based somewhat

on past experience that this girl will have a spontaneous remission without benefit of surgery.

MODERATOR CROHN: I hope so!

Dr. Garlock, someone would like to know whether surgery for ulcerative colitis always means ileostomy and complete colectomy?

DR. GARLOCK: Except for regional ulcerative colitis or right sided colitis, ulcerative colitis may be considered a universal disease involving both the rectum and colon. There are segmental varieties, but these are in the very small minority. It is my feeling from an experience of some 300 odd cases now treated surgically, that once you are committed to surgical therapy the job must be finished to include removal of the colon and also the rectum. I do not subscribe to the occasionally propounded proposal that, after doing an ileostomy for early ulcerative colitis, for instance, one could close the ileostomy at a later date without removing the colon or rectum. The results have been disastrous in this group of cases as the literature will inform you. We are therefore committed to a total job once an ileostomy is done.

MODERATOR CROHN: *Dr. Flood, someone would like to know if there are lasting cures with steroid therapy, particularly in the early cases? Are the results permanent? You mentioned it in your talk, but speak of it again in the early cases.*

DR. FLOOD: The largest series that I am aware of, in which the use of steroids has been reported, is that of Truelove and Witts in England, who treated about 100 patients including alternate controls with dummy tablets. They have reported that, after a period of treatment of six weeks with cortisone in the standard dosage, a follow-up survey about nine months later showed that in most instances there was no difference between the control group and the group who had been treated with steroids. However, in the patients who had the disease for only a short period of time, that is for less than two years, there seemed to be an advantage for those who had received steroid therapy.

MODERATOR CROHN: A few years ago the late Dr. Frank Lahey observed in one of his articles that, in his opinion, the use of steroids would eliminate emergency surgery in cases of acute fulminating ulcerative colitis. I myself am tremendously impressed with the striking effects of steroids properly applied to cases of fulminating colitis. Not so much in the chronic cases, but in acute cases the results are exceedingly striking.

While on the subject I should like to ask Dr. Garlock and Dr. Flood a question I have in mind. Much is heard about the increased risk of operation when the patient has been under prolonged steroid therapy. Dr. Flood, have you met this problem? I know Dr. Garlock has encountered this situation. I would like to know your views.

DR. FLOOD: With increasing experience, the fear of operating on the patient who is currently on steroid therapy has diminished a good deal, and it has become possible to operate on patients while maintaining steroid therapy throughout the procedure. In some instances there may be an apparent difficulty in wound healing if the patient is on steroid therapy.

MODERATOR CROHN: *Dr. Garlock!*

DR. GARLOCK: We have heard many stories about delayed wound healing and sudden collapse occurring on the operating table during the course of colectomy or the performance of ileostomy, yet we are seeing an increasing number of patients being treated preoperatively with steroids who must be operated upon subsequently.

I am frank to confess that I have been somewhat alarmed by the indiscriminate use of steroids and the unpredictable response of patients to major surgical procedures. I have in mind a patient who returned to the hospital the day before yesterday after a satisfactory recovery from a subtotal colectomy and ileostomy, who had been on steroid therapy and left the hospital after discontinuance of the steroid therapy. She was readmitted in adrenal collapse four or five days after she left the hospital. It was Dr. Crohn's quick recognition of this, followed by the administration of the proper remedy, that brought her out of her severe shock. I believe we are going to see more and more of this sort of thing unless we adopt preventive measures. These measures, I think, should include a continuation of steroid therapy both during operation and during the postoperative period followed by a gradual weaning process. How long this weaning process should take, I am sure I don't know, but I must admit I have many fears about the reaction of patients to surgical procedures after steroid therapy. The complete answer has not been given as yet.

MODERATOR CROHN: *I, too, don't know the full answer, but I have been very much interested in this question of so-called adrenal exhaustion due to cortisone therapy when patients are on the operating table. I don't know the physiology of it, but I see Dr. Gabrilove in the*

audience, and perhaps he, as an endocrinologist, can give us explanations concerning the action of ACTH and cortisone upon the adrenals and why the risk of operation is then so much greater. Dr. Gabrilove, will you explain to us the physiology and the effect of cortisone and why surgical risk should be greater?

DR. J. L. GABRILOVE: The adrenal cortex is driven by the elaboration of adrenal corticotropin from the adenohypophysis. If one administers glycogenic corticoids such as cortisone or hydrocortisone, or its derivatives, including the fluoro derivatives or prednisolone, one inhibits the pituitary elaboration of corticotropin. Therefore the pituitary elaboration of this hormone is set at rest. The adrenal is no longer driven and undergoes atrophy. If during this period of time, following the administration of adrenal cortical steroids and subsequent atrophy of the adrenal cortex as the result, one were to stop adrenal cortical steroid therapy and were to subject these patients to stress, we would find that the increased requirements for adrenal cortical steroids to combat this stress would be inadequate. As a result, the patient would develop a peculiar type of shock, which we have come to recognize as specific shock seen in adrenal cortical insufficiency which results in death. This was best demonstrated in patients with Cushing's syndrome who had had tumors, who were operated on a number of years ago. In these patients the tumor elaborated large amounts of glycogenic corticoid. Through a similar physiological mechanism the contralateral adrenal cortex was set at rest and atrophied. Following removal of the tumor the patients then died in 18 to 24 hours in shock, a shock unresponsive to the usual therapeutic measures of transfusion, plasma and intravenous fluids. Following the introduction of specific adrenal cortical steroids, particularly those available for parenteral use and specifically intravenous hydrocortisone, it was found that these patients could be saved by preparing them with large amounts of glycogenic corticoids preoperatively or, at the time they went into collapse, by the administration of large amounts of hydrocortisone intravenously. So I think the lesson that we have learned from this collateral evidence is that patients who are on adrenal cortical steroids may be operated on safely but that it is an error to discontinue steroids. We must treat these patients as if they had adrenal cortical insufficiency and since following operation their requirements are markedly increased, steroid administration must be *increased* rather than decreased. Following such a procedure, employing

large amounts of adrenal cortical steroids, similar to that used following adrenalectomy, you will find that the operative risk in these patients is no greater than in the ordinary patients with ulcerative colitis.

MODERATOR CROHN: Thank you very much, Dr. Gabrilove.

I should like to add that I understand it takes at least two or three weeks for the adrenal gland to regenerate itself after adrenal exhaustion, so that in the emergency of the shock of operation, cortisone must be replaced at the time. Intravenous Cortef is what is usually used on the operating table.

Is a gluten free diet of any use?

DR. ENGEL: Not to my knowledge; I don't know if anybody has tried it. I think there is always a non-specific effect of any technique of treatment you use. The evaluation of any new technique is fraught with great difficulty and I am interested to know, for example, that Dr. Crohn feels so strongly about ACTH. I wonder whether he does not underemphasize the weight of his name to his patients, that this is a complex of the adrenal cortex plus Crohn in the patient's eyes. I am not saying this facetiously because I think the significance of the physician who prescribes the medication is of great importance and that the physician who does not believe that ACTH or cortisone is a very good technique is bound to have much poorer results with it.

DR. GARLOCK: Mr. Chairman, I would beg to disagree thoroughly with that last statement!

MODERATOR CROHN: I too!

DR. GARLOCK: There is no question about the fact that, since the advent of ACTH, the picture of the clinical course of acute fulminating ulcerative colitis has changed markedly compared with what it was before. As Dr. Engel may remember from his association with our hospital not too many years ago, it is very rare for us to have to do an emergency ileostomy. With the use of ACTH we can now get these patients into better shape and do the ileostomy at a time of our own choosing, not as an emergency and as a last-resort measure. I think that has been the experience all over the country and I don't attribute it either to Dr. Crohn's presence or to any of the other doctors who are associated with the patients. However, I would like to stress again what Dr. Engel has said about the doctor-patient relationship and the successful care of ulcerative colitis patients. I think this also applies particularly to the surgeon. In my opinion, no surgeon will be

successful in the surgical care of the ulcerative colitis patient unless he accomplishes exactly what Dr. Engel has recommended, namely, a transference to the surgeon away from the mother, as Dr. Crohn has also emphasized, so that the patient begins to lean on the surgeon. Our best results have been obtained in that group of patients who accomplish such transference and we try to make it a regular part of the treatment. The surgeon must become an amateur psychiatrist himself but of a different variety than that of which Dr. Engel is talking.

I will cite one episode, if I may, which is the most dramatic I have ever known. This concerns a girl on the ward service of the hospital who had had an ileostomy and subtotal colectomy. I casually mentioned to her on rounds one day that I was going away on vacation in two weeks. From that day on she began to ulcerate the skin around her ileostomy. This progressed so rapidly that the day I left it measured about four inches across and finally extended to involve almost the entire abdominal wall. During my absence every known remedy was tried. They invited Dr. Frank Meleney down from Presbyterian Hospital because they thought this represented a microaerophilic streptococcus infection. Nothing that was used seemed to help in the slightest degree. One day one of my associates told her that I was returning on a certain date and from that day on the wound began to heal. It healed spontaneously within two weeks after I had returned. I cite this as an unusual example of what Dr. Engel was talking about. If I had not seen it with my own eyes I would not have believed it.

DR. ENGEL: I think we agree about too many things, Dr. Garlock, for me to leave the impression that I don't think the steroids are useful. There are many situations that have already been described in which they are extraordinarily useful. But my observation has been that with the second or third relapse, they become less effective. I believe that has been reported in the literature too. Dr. Flood may know that data better than I.

DR. FLOOD: Yes, I think that is true, Dr. Engel.

DR. ENGEL: This is not due to a pharmacologic change, but it has to do with the different expectation, the different readiness on the part of the patient, in the subtle sense, as Dr. Garlock has just described, in how he responds to the drug. It does not undo the pharmacologic effect but it is still different. The first time given, the patient responds quickly to the drug-induced improvement with a tremendous upsurge

of optimism and confidence in the doctor. This combination has a powerful therapeutic effect and is felt by the patient (and sometimes the doctor, too) as almost magical. Often the patient equates this with cure, so when a relapse occurs, the patient suffers an additional disappointment. On the second occasion the magic is gone and only ACTH is left.

MODERATOR CROHN: I think you are quite right, Dr. Engel, in both ways. The most interesting case I ever witnessed was that of a girl of 17 who had been raped during the war. Within 24 hours she developed the most severe fulminating ulcerative colitis that I have ever seen. After a few days, when she was reassured that she had no venereal disease and was not pregnant, she made a very rapid recovery. I think that is a most striking incident in which the psychosomatic insult produced the disease and the events following psychotherapy caused a cure of the malady.

I have two more questions, if we can confine ourselves to brief answers. Dr. Flood, is ulcerative colitis associated with arthritis and what would be the effect of a radical operation?

DR. FLOOD: Multiple arthritis is a common accompaniment of nonspecific ulcerative colitis. As I understand it, from those who have studied the type of arthritis which occurs in this disease, it resembles but is not identical with rheumatoid arthritis. In most instances it is characterized by pain in multiple joints without the development of any marked deformities. Marie-Strümpell's arthritis is also a rather common accompaniment of ulcerative colitis. Removal of the colon in patients with arthritic symptoms usually is followed by a relief of those symptoms.

MODERATOR CROHN: In my experience, complete and prompt relief.

There is one more question addressed to Dr. Garlock. Someone in the audience wants to know whether Dr. Garlock believes the total colectomy and ileostomy should be accomplished in one stage, as advocated by some of the more radical surgeons throughout the country, or whether he limits himself to ileostomy and partial colectomy?

DR. GARLOCK: This is also a "spiked" question. All I can say is that I have not been impressed by this radical approach as the method of choice in the surgical treatment of ulcerative colitis. If this philosophy were to be universally adopted, we would note an enormous morbidity and mortality. I am afraid it will still be necessary to exercise the best surgical judgment to choose the appropriate operation for the specific

situation at hand. As my experience increases, I become more convinced that we have made errors in the direction of trying to do too much at one sitting. I still believe very definitely that there are many patients who should be accorded the operation of ileostomy alone without any attempt to take out the colon. If we remember this we will lose fewer patients than by going overboard on the so-called radical maneuver that is being advocated in some quarters. Of course, if you have a patient with chronic ulcerative colitis who is not too debilitated and who can withstand a subtotal colectomy, it does not take too much extra time to take out the rectum also. However, I am very much opposed to four to six hour operations in the treatment of ulcerative colitis.

DOCTOR: I am interested particularly in the case where hemorrhage is the predominating factor. How far would you go?

DR. GARLOCK: It all depends upon the condition of the patient at the time of operation.

DR. ENGEL: May I reverse the procedure and ask someone in this audience a question?

MODERATOR CROHN: Yes.

DR. ENGEL: I see Dr. Lyons in the audience. I know he has had great interest in ileostomy clubs, and others might be interested in this too. Where patients have been active in the clubs for five or six years, what is the morbidity rate among patients both in respect to the development of complications of ileostomy including ileitis, and in respect to other types of illnesses? Does he have any impressions about the morbidity and mortality of this group of patients versus the ileostomy patients who do not participate in this type of social group? I have the feeling that the ileostomy clubs have provided a very significant type of interpersonal relationship which may be a major health-securing factor to these patients.

MODERATOR CROHN: *Dr. Lyons, would you like to come to the platform and answer that question? I believe most of our members in the ileostomy club have had colectomies rather than simple ileostomies.*

DR. LYONS: Regarding the complications of stoma, the figures vary according to the section of the country from which reports come and the way one evaluates complications, but I would say about one out of three ileostomy patients has some major complication. However, the mortality from these major complications is not high.

As far as the second question is concerned, I would say of course

it makes a great deal of difference whether a patient has a relationship with other individuals with ileostomy. There are now over a dozen ileostomy clubs in this country and in Great Britain, and so, really no patient who has an ileostomy should be prevented from having this experience of attending meetings with other ileostomy patients. Unquestionably they not only do better surgically but they also become useful individuals whereas sometimes, when left to their own devices, they are miserable and useless.

MODERATOR CROHN: That, I think, is important.

I was interested to hear Dr. Flood say that he also was having experience with ileitis and ileo-jejunitis following ileostomy and colectomy, something which is quite new in medicine. Have you noted a fairly high incidence and had a large experience with that, Dr. Flood?

DR. FLOOD: You mean in patients who have had a colectomy?

MODERATOR CROHN: *That is right.*

DR. FLOOD: And have an ileostomy?

MODERATOR CROHN: *Who previously did not have ileitis.*

DR. FLOOD: I don't think I can quote figures, but it is a common problem in our experience.

MODERATOR CROHN: *Isn't that astonishing! That is new, isn't it?*

DR. FLOOD: It is a very difficult situation to manage. There are many things which happen in the terminal ileum, after ileostomy, which are poorly understood. One of the commoner complications is something which has been called ileismus, that is to say abdominal cramps, and which produces discharge from the ileum for a period, and this appears commonly in the early period after operation in many patients. Other individuals may develop frank evidence of ileitis or even perforate. Whether these patients have had a certain amount of ileitis unrecognized at the time of operation is not agreed upon. Whether it represents an extension of the disease upward after the operation is another possibility, but the events that go on in the ileum after ileostomy are very difficult to understand.

MODERATOR CROHN: It is time to close this meeting and I should like to thank the panelists for their cooperation and the audience for its attention and interest.

SURGICAL CARE OF THE CONFEDERATE STATES ARMY*

RICHARD B. STARK

Assistant Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon in charge of Plastic Surgery, St. Luke's Hospital in the City of New York.

and

JANET C. STARK

INTRODUCTION

On April 2, 1865, a courier handed President Jefferson Davis a note as the President of the Confederate States of America was attending services at St. Paul's Church in Richmond, Virginia. President Davis flushed portentously, rose to his feet, and left the church. Petersburg had fallen; the siege of Richmond had been lost. Soon the exodus from Richmond began, and, with it, the southern end of the city was fired. Tobacco warehouses burned, as did two important houses, which, with their contents, were completely destroyed. One of these was the office of Surgeon-General Samuel P. Moore, and the other was the house adjacent, in which were stored records and reports, pertinent to his office, that had been accumulating for the four years of the War Between the States. Following the loss of this invaluable material, the preparation of an adequate history of the Medical Corps of the Confederate States Army, or even of a complete roster of its personnel, became an impossible task.[1]

The Scope of the Problem of the Medical Corps of the Confederate States Army. The Medical Corps of the Confederate States Army was made up entirely of general practitioners who had served in all parts of the South during their professional lives in the preceding period of unbroken peace, and this left them totally unprepared for the vast

* Presented before the Section on Historical and Cultural Medicine at The New York Academy of Medicine, March 27, 1957. Manuscript received May, 1957. (Portions of this paper were presented before the New York Civil War Round Table, April 9, 1957, and before the Annual Spring Clinic, Norfolk (Va.) County Medical Society, March 28, 1956.)
This work was aided by a grant from the W. Alton Jones Foundation and USPHS Grant No. D-319.

amount of traumatic surgery which they were to face. Little, too, did they know of field sanitation. To add to their problems, the armies, collected hastily to repel invasion, were fed deficiently, were poorly equipped, and were paid almost not at all. However, in spite of virtually no surgical equipment and no textbooks on surgery, this small but valiant corps of army surgeons, with their assistants and their ancillary corpsmen, made an heroic and enviable record throughout the horrible four years of suffering which became an inseparable part of the army of the South. How well the leaders of the Medical Corps of the Confederate States Army overcame these basic obstacles will be seen. However, the statistics of diseased and wounded, when compared with those of the North, bring this story into focus with accent upon its epic proportions.

Confederate forces actively engaged in the four-years' War Between the States numbered no more than 600,000 troops. This small force faced a total number of 2,800,000 soldiers mustered into the Northern Army, or approximately four times the fighting contingent of the Confederate States. Of these 600,000 Confederate troops, 54,000 were killed outright and approximately 200,000 died either from wounds of battle or from disease. Another 200,000 were lost to the Confederate States Army as prisoners of war because of the policy of non-exchange of prisoners adopted and enforced by the United States. Approximately 100,000 were discharged because of disability from wounds, disease, or desertion during the war years. Of this small force, horribly decimated at the end, approximately 3,000,000 cases of wounds and disease were cared for by the Medical Corps of the Confederate States Army. Thus, on an average, each Confederate soldier was disabled by wounds and sickness about six times during the war![1] On April 9, 1865, as the war ended, General Lee could not muster 10,000 men who were fit for active warfare from his former great army of northern Virginia. Dick Ewell surrendered with only 8,000 men to Phil Sheridan.

In contrast to the statistics of killed and wounded is the shockingly high figure of losses due to illness in the field. The troops of the Confederate States Army were drawn from rural districts and had never been exposed previously to contagious illnesses; thus, exposure from crowding made contagion a frightful scourge of the army. Measles, a disease regarded lightly under ordinary conditions, struck terror in the Civil War camps, for its sequelae were pneumonia and phthisis. Erup-

tive diseases, glandular affections, tuberculosis, capillary bronchitis, typhoid and malarial fevers, diarrhea, and dysentery were the chief causes of mortality and deterioration of strength in the Confederate States Army[2]. Aiding and abetting natural exposure of this type were fatigue, deficient food which was often spoiled, clothing which was often ragged or lacking, no water purification, poor shelter, exposure to sudden changes of temperature and to dampness and wetting, as well as indifference to or ignorance of field sanitation.

Drugs and Instruments. The desperate shortage of medical supplies and instruments which resulted from the Union blockade necessitated heroic improvisations. "To supply medicines which were declared by the enemy to be contraband of war, our Medical Department had to seek in the forests for substitutes and to add surgical instruments and appliances to the small stock at hand as best they could."[3] When Fort Sumter was fired upon, the entire male student body of the University of South Carolina joined the Confederate States Army, while the faculty became the pharmaceutical house for the Confederate States Medical Corps. The principal text in pharmacology was a war-time book prepared by Dr. Francis Peyre Porcher, Professor of Materia Medica and Therapeutics at the medical college in Charleston. This text was entitled, "Resources of the Southern Fields and Forests, Medical, Economical, and Agricultural, Being Also a Medical Botany of the Southern States, with Practical Information on the Useful Properties of the Trees, Plants and Shrubs."[4]

The number of skilled instrument makers in the Southern States was small. There were, however, purchasing agents in London and in Nassau whose duty it was to purchase and forward supplies which were otherwise completely unobtainable. In addition, raids upon the relatively unguarded Northern supply lines were frequent during the early part of the war at a time when the cavalry of the South was superior. One such raid netted the cavalry of Nathan Bedford Forrest a cache of medical supplies estimated to be worth $150,000. Too, smuggling of quinine and morphine was common by southern ladies who secreted these drugs amongst their many petticoats as they crossed the lines[5].

Texts. Textbooks were scarce, and scientific intercourse with foreign countries came to a virtual halt. To fill this intellectual gap, two excellent manuals of military surgery were published, one in 1862 and

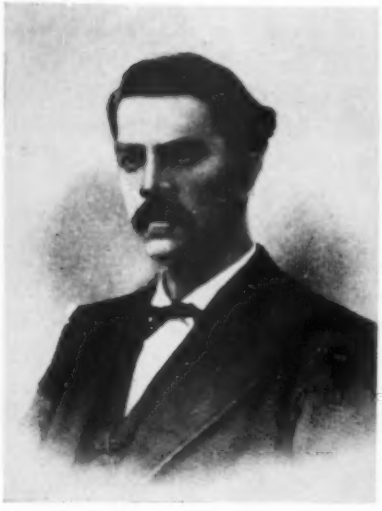

Fig. 1

Fig. 2

Fig. 3

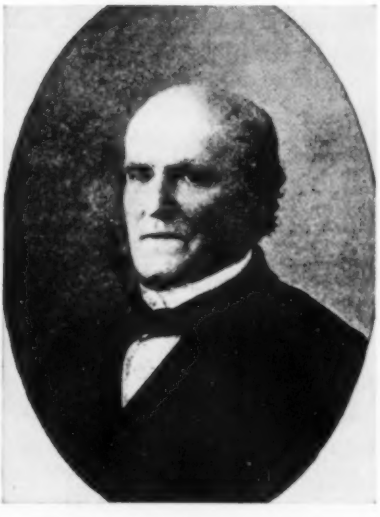

Fig. 4

[LEGENDS ON OPPOSITE PAGE]

one in 1863[2, 6]. Beginning in 1864, the "Confederate States Medical and Surgical Journal" was issued monthly for fourteen consecutive numbers. This reached the hospitals and occasionally got into the field. In this excellent journal, original articles were printed with abstracts of recent foreign periodicals, offering the reader an epitome of military medical experience in the North and the South, as well as of the current literature in peaceful European countries[7].

Organization of the Medical Corps. Shortly after the outbreak of the War Between the States, President Jefferson Davis appointed Samuel Preston Moore of Charleston, South Carolina, the Surgeon-General. As Surgeon-General of the Confederate States Army, Moore organized an efficient medical and surgical department. It was necessary for General Moore to establish large pharmaceutical laboratories to convert indigenous plants and barks into drugs which could be used by the Medical Corps. It was necessary for him to promote and administer the manufacture of surgical instruments and appliances. It was he who

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Fig. 1—The most colorful surgeon in the Confederate States Army was Hunter Holmes McGuire, M.D. While a medical student in Philadelphia, McGuire led a revolt of about 300 Southern medical students, who left schools in the North for ones in the South at the time of the John Brown episode. As Medical Director of "Stonewall" Jackson's corps, McGuire was held in high esteem by his commander, who mentioned him often in his dispatches. It was McGuire's sad task to have to amputate General Jackson's arm after the latter was wounded accidentally at Chancellorsville. The operation was successful, but Jackson died of a complication upon his eighth postoperative day.

McGuire, with Jackson, was responsible for first release of captured Union Army surgeons, a practice—adopted later by both the North and the South—which antedated formation of the Red Cross. McGuire worked hard in the post-war period to eradicate from history books the story of the Civil War which had been slanted towards the Northern point of view. A leader in his field as well as a master surgeon, McGuire was honored by being made president of the Southern Surgical Association, A.M.A., and the American Surgical Association.

Fig. 2—Captain Sally B. Tompkins, C.S.A., was the only woman commissioned by the Confederacy. A philanthropist and humanitarian, Sally Tompkins established and maintained financially the Robertson Hospital in Richmond, which made an enviable record. An executive order was issued early in the war, placing all private hospitals under government control, but, because this order threatened to lose the Confederacy a needed benefactor, President Davis commissioned Sally Tompkins a captain in the Confederate States Army. Miss Tompkins accepted the commission but refused to place herself on the payroll.

Fig. 3—J. B. Bean, M.D., D.D.S. was a contract dentist from Chattanooga whose intermaxillary wiring revolutionized the care of jaw fractures and presaged modern care of these injuries.

Fig. 4—Superintendent of Hospitals of the C.S.A., S. H. Stout, M.D., had been in charge of Gordon Hospital in Nashville and of hospitals in Chattanooga, and proved himself an extremely able and tactful administrator. It was stated that, because of Stout's medical organization, Johnston's army was strengthened by at least a full division of fighting men. Stout became Medical Director of the Hospitals of the Department and Army of Tennessee.

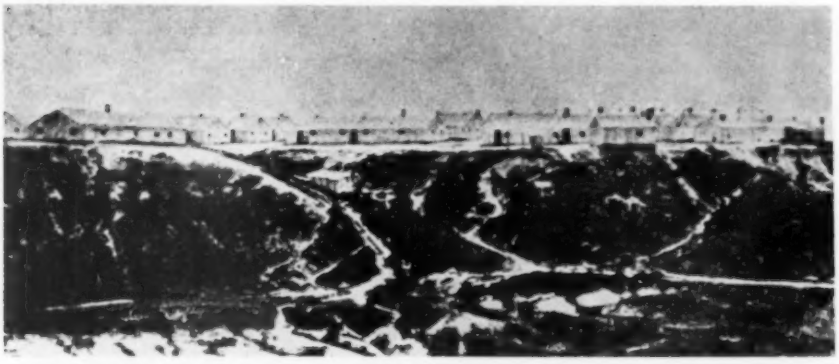

Fig. 5—With 8400 beds, the Chimboraza Hospital is reputed to be the largest ever to exist on this continent. Built upon heights of the same name, Chimboraza, with the Jackson and Winder Hospitals, was one of three largest hospitals in Richmond. A vast hospital center, Richmond had 15 named and 27 numbered hospitals within its environs.

Fig. 6—A general hospital in the Confederacy. These hospitals were usually composed about equally of buildings and Sibley tents of the tepee type. Patients were segregated according to their state of origin, after a suggestion of Representative James Farrow of South Carolina in 1862, which became law. This segregation was intended to mitigate feelings of homesickness.

Fig. 7—With defeat at Petersburg, in April, 1865, the Siege of Richmond was lost. Rather than let the city fall intact into Union hands, Richmond was fired. About a tenth of the city burned, but, tragically for the purposes of this chronicle, the Surgeon-General's office and the repository for records of the Medical Corps of the Confederate States Army were amongst the buildings destroyed. Because of this, the story of medicine and surgery in the Confederacy cannot be told authoritatively. A complete roster of the Medical Corps, or even its strength, is not known.

established a large and efficient hospital service and a field ambulance corps. Jefferson Davis stated, "It would be quite beyond my power to do justice to the skill and knowledge with which the Medical Corps performed their arduous task. I regret that I have no report which would enable me to do justice to the officers of his [Samuel Preston Moore's] corps, as well in regard to humanity as in their professional skill."[3]

The Quartermaster Branch, or purveyor section of the Medical Corps, was established by Dr. Thomas H. Williams.

Although an active roster of the medical corps is not available, usually each separate command engaged in the field had one surgeon and two assistant surgeons, so if one added units not in the field to those actively engaged in combat, it is estimated that there were approximately 2,000 surgeons and 4,000 assistant surgeons, or a total of 6,000, which comprised the Medical Corps of the Confederate States Army[1].

"More than 3,000,000 cases of wounds and disease were cared for by the Medical Corps in the Confederate States during the war, in addition to which were the 270,000 Union soldiers held as prisoners of war. The efficiency of the department is shown in part by the fact that the percentage of deaths of Union prisoners of war in the Confederate prisons was little more than 8 per cent, while the percentage of deaths of Confederate prisoners of war in Northern prisons was more than 12 per cent."[2]

At the outbreak of the war, the organization of the Confederate Medical Department was identical with that of the United States Army. There was a surgeon-general with the rank and the pay allowances of a brigadier-general, and there was a medical director in each army corps or department with the rank of colonel. In each division was a chief surgeon (who consolidated reports sent in by senior surgeons), regiments had a surgeon, who was a major, and an assistant surgeon, a captain, assigned to them. A battalion and sometimes a company of artillery had a captain as an assistant surgeon assigned to them. The services of contract surgeons were provided for. These were civilian physicians who served with pay and allowances of a second lieutenant.

Medical officers were charged with the examination of recruits, who were stripped so that the "free use of their limbs could be observed". It was to be noted whether or not the "chest was ample" and whether the hearing, vision, and speech of the recruit were perfect. The

Fig. 8

Fig. 9

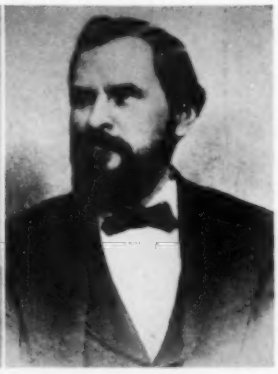

Fig. 10

Fig. 8—While the North was experiencing growing pains in its Medical Corps and was commanded successfully by four Surgeons-General, the South was blessed with an incredibly astute and efficient Surgeon-General in the person of Samuel Preston Moore of Charleston. Moore had been a surgeon in the "old army" but had resigned to join the Confederacy. Although there were several "paper" Surgeons-General serving initially for several weeks, Moore organized an astonishingly effective Medical Corps in a South that had no surgical instrument makers, no textbooks of surgery, no manufacturers of prostheses, and no drug houses.

Fig. 9—James Brown McCaw, M.D., a youthful professor of chemistry and pharmacology at the Medical College of Virginia, was given the task of building and administrating the Chimboraza Hospital in the hospital center of Richmond. McCaw was editor of the Confederate States Medical and Surgical Journal, as well, and during this period of intense activity six scientific articles appeared in this journal from the staff of his own Chimboraza Hospital.

Fig. 10—J. J. Chisolm, M.D., wrote one of the two badly-needed textbooks on surgery used by the Confederate Medical Corps. His *A Manual of Military Surgery* promulgated rules of field sanitation as well as principles of operative treatment of traumatic wounds.

recruit was to have no tumors, ulcerations, extensively cicatrized legs, rupture, or chronic cutaneous affections. He should not have received any contusion or wound to the head previously. It was to be ascertained whether or not the recruit was a drunkard or subject to convulsions or infectious disorders. In giving certificates for discharge because of disability, medical officers were counselled to take particular care that none of the illnesses (such as epilepsy, convulsions, chronic rheumatism, derangement of the urinary organs, or ulcers) were feigned or purposely produced, but even with these definitive admonitions and in spite of the induction physical examination, many women, masquerading as men, were inducted into the service.

The duties of the surgeon included care of the sick in camp and establishment of field hospitals upon the march. As soon as it was learned from the commanding officer where the troops were to engage in combat, a site for a hospital was chosen, preferably behind a hill or in a ravine for defilade, approximately one-half to one mile in the rear of the line of battle. The wounded were brought from the front on stretchers or in ambulances by members of the regimental band which comprised the infirmary detail whose modern counterparts are the Company Aid Men. The combined medical staff of the brigade or division performed necessary operations. The assistant surgeons were in the rear of the regiment, but in front of the field hospital, giving first aid to the wounded. The dressing station was the forerunner of the Battalion Aid Station. Assistant surgeons adjusted and temporarily cared for fractured limbs, controlled hemorrhage, gave drugs to relieve pain, and made certain that the wounded were carried promptly to the hospital by the infirmary detail or ambulance corps.

The hospital steward, with the pay and rank of a sergeant, was in charge of hospital stores. Usually he was an undergraduate of a medical college with previous experience in the handling of drugs. Cooks and nurses were under the steward and were subject to military control. Ward masters were in charge of personal effects of the patients. In a general hospital there was one steward, one nurse, and ward master, plus one nurse to tend patients. One laundress was provided to 20 and one cook to 30 patients.

The uniform worn by the Medical Corps was similar to that of the line officers, except that the facing of the collar and cuffs was black, while that of the infantry was light blue, that of the artillery scarlet, and that of the cavalry buff. In front of the cap of the military surgeon were the gold letters "M.S." (Military Surgeon), flanked by two olive branches.

It was felt by some that because of the easy manner in which commissions for medical officers were obtained, many were not qualified. However, commissioning boards were established which gave practical examinations to prospective medical officers as well as to those already in the service. The medical knowledge, moral habits, and physical qualifications of the candidates were examined. One such board was headed by Dr. Chaille, later Dean of Tulane University, who stated, "The incompetents were exceptions to the superior merit of the vast

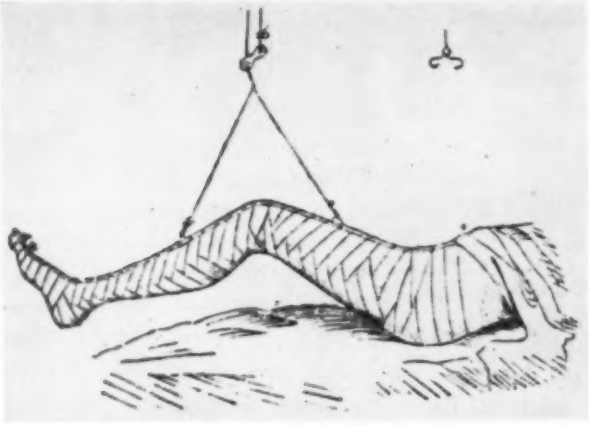

Fig. 11—Of the soldiers who were wounded and reached hospitals, 70 per cent received wounds of the extremities. From experience gained earlier in the Crimean War, it was known that, in the pre-Lister days of the Civil War, one's chances of recovering from a fracture of a long bone were greater if the limb were amputated. Dissatisfaction grew over what was considered by many surgeons as an unnecessary amputation of limbs. James Bolton, M.D., devised a form of extramedullary fixation which anticipated the present Roger-Anderson apparatus, and Professor Nathan R. Smith of Baltimore devised a conservative form of therapy consisting of an anterior wire splint (shown above) which was suspended from an overhead frame.

Fig. 12—Because of the dearth of textbooks upon medicine in the Confederacy, Surgeon-General Moore published the "Confederate States Medical and Surgical Journal." This excellent journal was issued monthly for fourteen numbers, until March of 1865. Only two libraries in this country possess all fourteen issues of this journal.

majority of the members of the Confederate staff."[8] It was felt generally that the students of the South who had graduated from medical college prior to the onset of the war were better trained than those who were graduated in subsequent years. Dr. Samuel H. Stout, Medical Director of the Department of the Army of Tennessee, said, "When I attended lectures in Philadelphia more than half a century ago, the number of students in the two schools there [University of Pennsylvania and Jefferson] was a little more than 1000. More than half of them were from the Southern states."

Rations and Field Sanitation. The supply of food and water for the troops was established by the Confederate command and promulgated in Chisolm's *Manual of Military Surgery*[2]. Methods of clearing turbid water in the field and of making it potable were suggested. Stagnant or ditch water was to be boiled with a lump of charcoal. A piece of alum was thrown into turbid water to settle it and remove the deposit. It was suggested that water for large units be filtered through a barrel filled with straw.

One ration consisted of three-quarters of a pound of pork or bacon, one and a quarter pounds of fresh or salt beef, 18 ounces of bread or flour, 12 ounces of biscuit, and one and a quarter pounds of corn meal. As a result of discoveries made during the Crimean War, it was suggested that, in the temporary absence of fresh vegetables, lime juice or citric acid be used to prevent scurvy.

Sanitation. Unhappily, many regimental camps were accumulations of filth of every description, the odor of which could be detected from great distances. A strong appeal was made to the men for the use of unit latrines. It was suggested that latrines be placed at least 100 yards from the tents and on the down-wind side. It was suggested also that the privies be established over water. This was before the advent of bacteriology, and, hence, pollution of the water supply by sewage went unrecognized and was partially responsible for the dreadful morbidity and mortality from diarrheic and dysenteric diseases. Regulations dictated that latrines were to be prepared immediately upon the establishment of camp, and the men were compelled to use them under penalty. Penalties were rarely imposed, however, and the inconvenience of travelling to a distant latrine was avoided with relative ease by using the camp site.

Field Pack. The best check list for the field pack was that of Stone-

Fig. 13—To supply surgical instruments, needed so desperately, the South maintained purchasing agents in Nassau and in London. Instrument sets like the above were the work of English manufacturers, and were run through the blockade. Ironically, the North proved to be a good source of supply for medical material as, in the early part of the war, the superior cavalry of the South obtained large caches of equipment and drugs from raids on Northern wagon trains—(From The Authors' Collection).

wall Jackson, whose men covered such amazing distances on forced marches. Jackson insisted that full field equipment consist of two flannel shirts; two pair of woolen socks, flannel drawers, and shoes; one pair of gaiters; a small case of needles and buttons for mending clothes; a shoe brush with blacking; a comb and hair brush; a tooth brush; one piece of soap; a sponge for washing the body and a towel for drying it; two pocket handkerchiefs; an overcoat; a heavy blanket; and two yards of India rubber cloth to protect the soldier from inclement weather. Jackson stated, "When a person has not more than one change of raiment, the strong impression of *necessity* obliges him to prepare for the return of want. When there is a superfluity, the necessity

does not present itself so forcibly, and, hence, the dirty clothes are crammed into the knapsack, where they accumulate in quantity, not obliging the individual to recollect that they are *not* for use unless they are washed."[2] Jackson made no mention of shaving equipment, for he felt that, "Every soldier in the field should allow his beard to grow. . . . [as] it protects his throat and often prevents lung diseases [and] catarrhal afflictions . . . a heavy mustache is known to protect the wearer to a certain extent from malarial influences, acting as a sieve to the lungs."[2]

Anesthesia: The Care of Wounds. Ether, nitrous oxide and chloroform had all been discovered and used extensively prior to the War Between the States. Chloroform had been used 25,000 times previously in the Crimean War with no unfavorable results, and was the anesthetic agent of choice in the War Between the States. Dr. Hunter McGuire, Medical Director of Jackson's Corps, collected 15,000 cases of chloroform anesthesia during the war without a single death[5]. Although the blockade of the Southern states was most effective, chloroform, quinine, and morphine were never completely lacking in the Confederacy during the war.

Preoperatively, the patient was given a light, nutritious meal in the hope that the stomach would then be empty and the patient strong. Brandy was the premedication of choice. The patient was placed in the supine position, and chloroform was poured upon a cloth cone. The anesthetist and the assistant were completely silent during the induction. Corneal reflexes were tested to determine complete anesthesia of the patient. The pulse, respirations, and color of the patient were scrutinized closely. If the airway became obstructed, the tongue was seized (by a hook, tenaculum, forceps or fingers) and was brought forward[6].

Asepsis. Antisepsis and asepsis were not understood at the time of the War Between the States, as the discoveries of Lister came, ironically, in 1865, as the war ended. Instruments were always unsterile, and wounds were cleaned with an unclean sponge which was used indiscriminately in all cases. So common was the appearance of suppuration or "laudable pus" upon the fourth day that its appearance was thought wrongly to herald the progress of a wound which was healing normally, always by secondary intention.

Minie Balls. A large portion of the injuries of battle were brutal wounds caused by the Minie ball, a conical rifle bullet named for its

inventor, Captain C. E. Minie of France[9]. The low velocity of the Minie ball accounted for its destructive qualities, which produced most injurious wounds. With low velocity, the conical ball would turn in its course, causing a bursting type of wound of exit. These wounds were much more severe than those caused by bullets of higher velocity which passed completely through the soft parts and bones without turning broadside.

Treatment of the ordinary wound of battle consisted of shaving the part, sponging it with warm water, probing the wound, and removing foreign bodies, which, it was hoped, would include the missile. The wounds were dressed with lint, the scrapings from cotton. Wet dressings were applied often, using cotton dipped in cold water. These were used routinely in large wounds, amputations, resections, and extensive lacerations. The wet dressings were used in three different ways: by direct application, by application which was sealed so as to prevent the evaporation and to exclude air, and by cold water which was dripped onto the wound[10]. Flaxseed or bread poultices were employed often. Raw cotton, baked or charred in the oven, was used also for dressings and hence was rendered relatively aseptic by this method of treatment. Cotton, flax thread, silk, and horsehair were used as ligatures. The horsehair was boiled to make it more pliable and soft, and thus, accidentally, was rendered sterile.

The Treatment of Hemorrhage. Hemorrhage was a major problem of the wounded of the War Between the States. "Three-fourths of those who died in battle perish from hemorrhage." [6] It was stated, "No class of operations demands a more accurate knowledge of anatomy than those upon the arteries: no class in which perfect equanimity is so important to the surgeon: and no class, the attendance of which are more calculated to alarm, disconcert and confuse." [6] Hemorrhage itself was divided into primary and secondary hemorrhage.

Secondary hemorrhage was subdivided into several types: "*retarded hemorrhage*" (eight to ten hours following injury—it was stated that following the engagements around Richmond, in the Peninsular campaign, a very large number of the wounds began to bleed freely after the patient arrived at the hospital); "*intermediate hemorrhage*" (three to five days following injury without any antecedent hemorrhage), and "*consecutive hemorrhage*" (eight to fifteen days following surgery when the separation of slough opened a vessel injured previously or

softened by the process of necrosis).

The treatment of hemorrhage was divided into provisional means and operative means. Provisional or conservative means consisted of pressure, elevation, and application of sedation, cold, and local styptics. Pressure was exerted either by hand or by the application of a tourniquet over the course of the main artery proximal to the injury, with the object of flattening the vessel and of obliterating its lumen. Styptics of persulphate and perchloride of iron (Monsel's solution) were used. No operative intervention was performed unless the vessel had bled, as injury per se, without external bleeding, was not an indication for operation. Secondary operation was performed only at the site of injury, when both ends of the severed vessel were ligated.

The Care of Wounds of the Extremities. Seventy per cent of those who lived to reach a hospital had wounds of the extremities. From experience in the Crimean War, it was well known to all Confederate surgeons that a gunshot wound into any joint or a gunshot fracture of the femur was nearly always fatal if *not* operated upon. Statistics from the Crimean campaign showed that *only* 19 of 194 patients (10 per cent) with compound fractures of the femur recovered if the limb were left untreated. However, when amputation was resorted to, 12 per cent recovered from fractures of the proximal third of the femur, 40 per cent recovered from fractures of the middle third, and 43 per cent recovered from fractures of the distal third. Consequently, early in the war, the rule was established of amputating the extremity if it were injured seriously, for it was thought that primary operation gave the best chance for recovery. Because of this surgical premise, thousands of limbs were sacrificed that could have been saved at the present time. In fractures of the upper third of the femur, the dangers attending amputation were so great that it was questionable whether amputation was indicated. In gunshot wounds of the upper extremity, as much of the hand as possible was preserved if amputation were resorted to[6]. It was suggested by J. S. Wilson[11] that resection of the proximal segment of the humerus be performed following fracture, thus allowing the muscles of the upper arm to function in an unimpaired manner, although reducing the arm to a mere flail.

"In standard methods of amputation, the integument is divided by circular, elliptical, or hemi-elliptical incisions: or by a combination of the first and last forms." [6] If the amputation were performed using only

the knife, it was spoken of as having been performed "in contiguity". If section demanded the use of the saw or bone-biting forceps, it was said to have been performed "in continuity"[6].

James Bolton wrote during the War Between the States of the unnecessary loss of extremities, stating that amputation was only an exchange of death by exhaustion for death by shock. "If the limb be saved, it will almost certainly be shortened, and frequently misshapen; and this may happen to such an extent that the limb may be an incumbrance." As a result of his dilemma, Bolton[12] devised an ingenious form of extramedullary fixation in 1864. Through two stab wounds in the soft tissues, holes were drilled in the cortex of the long bone. Rods were screwed into these holes. A longitudinal rod was then passed at right angles through the two upright rods outside the integument, parallel to the shaft of the bone. This method was the antecedent of the present-day Roger-Anderson apparatus.

An ingenious method of splinting was devised by Professor Nathan R. Smith, of Baltimore[13], consisting of bandaging the limb to an anterior wire splint and suspending the extremity from an overhead frame. The splint was made of wire and easily applied.

Statistics upon amputations reported in 1864 in the Confederate States Medical and Surgical Journal stated that there was a mortality from 1814 operations for amputation, resection, and disarticulation of 34 per cent. There was a mortality from primary amputation for fracture of the femur of 38 per cent, and a mortality of 73 per cent from secondary amputation. In amputation of the leg, there was an attendant mortality of 30 per cent for primary amputations and 49 per cent in secondary amputations. In amputations of the upper arm, there was a 14 per cent mortality for primary amputations and 37 per cent for secondary amputations; primary amputation of the forearm carried with it a 12 per cent mortality and a secondary amputation a mortality of 22 per cent.

By 1864, there were nearly 10,000 amputees in the Confederate States Army. Although artificial limbs were being manufactured at that time for lower extremity amputees, the manufacturers could supply only one-tenth of the demand. Ideally, amputation stumps were left long enough to secure abundant leverage, were well covered with soft tissues, and were shaped like a truncated cone. The socket of the artificial limb was well padded and was fitted to the stump so that every portion

of its periphery was in contact except the tip of the stump. "Artificial limbs resemble those of the resecta except that the *skeleton is without.* Their structure generally is of wood, covered with leather, but sometimes of a heavy wire cloth. Strong and well-secured joints at points corresponding with those in the host's limb, move with ease and exactness through the medium of cords, levers and springs of metal or guttapercha, the whole being, in symmetry and function, a faithful representation of the natural leg, with the exception that the artificial leg, being but the work of man, is a more simple apparatus." [14]

The Care of Abdominal and Chest Wounds. Approximately 20 per cent of the wounds incurred were of the torso. Abdominal wounds which perforated a hollow viscus were almost uniformly fatal. Although the pathologic physiology of sucking wounds of the chest was imperfectly understood, Assistant Surgeon Howard, of the United States Army, publishing in the New York Medical Times, suggested that gunshot wounds of the chest be treated by sealing hermetically the wounds of entrance and exit, thus preventing the additional entry of air into the pleural cavity which would collapse the lung[15, 16].

The Care of Wounds of the Head and Neck. Ten per cent of the wounds of battle were of the head and neck. It was known during the time of the War Between the States that the great vascularity of the structures of the face promoted healing, and that bony fragments attached by periosteum would survive. Hence, debridement of bony spicules in the face was reduced to a minimum. It was known, also, that because of the vascularity of the face, serious hemorrhage might accompany all injuries in that area.

Fractures of the mandible were treated early in the war with a pasteboard splint designed by S. H. Stout, Medical Director of the Army of Tennessee. The problem of oral secretions was troublesome, although positioning of the patient was recognized to be important. It was felt that swabbing the mouth frequently was an advantageous procedure.

Stout, who was in charge of hospitals in Tennessee, utilized the services of Dr. J. B. Bean, a Chattanooga contract dentist who advocated splinting by intermaxillary wiring. Dr. Bean suffered from "chronic rheumatism" and hence was not upon active duty. Both Stout and Dr. Westmoreland, professor of surgery at the medical college in Atlanta, availed themselves of Dr. Bean's skill in the treatment of gun-

shot fractures of the mandible. It was never possible for Dr. Stout to place a dentist in every hospital, however, a number of civilian contract dentists were employed, as Dr. Bean had been, and funds were made available for them to work upon the problem of jaw fractures. Dr. Stout stated, "The result of their [Dr. Westmoreland's and Dr. Bean's] joint labors was so satisfactory, so perfect in its adaptation to the treatment of gunshot fractures of the lower jaw, that it had never before been equalled in the securing of comfortable articulation of the subject of the fracture while under treatment. . . . While inspecting the hospital, Dr. Westmoreland introduced me into what he called his 'broken jaw ward,' where I was greeted with great hilarity by the patients, who were able to converse freely and distinctly with me." [17]

It was recognized that wounds of the face were often more distressing than dangerous, because of the deformity that they caused. The larynx and trachea were injured often and, although tracheotomy was resorted to in cases of diphtheria, it was not used in cases of traumatic airway obstruction by the Confederate States Medical Corps.

It was known that because of the rich vascular supply, injuries to this region were often followed by dangerous primary or secondary hemorrhage. For hemorrhage of an exsanguinating type, pressure and powerful iron styptics were advocated. It was stated, "We find, after every great battle, the neck perforated by balls in every direction, accompanied by violent hemorrhage; yet, with the first fainting brought on from shock and loss of blood, we find a spontaneous cessation of bleeding, and the onward progress of the case becomes one of continued convalescence to perfect cicatrization."[2] McLeod reported on 128 cases with from slight to severe injuries of the neck, with but four deaths[2].

Severe hemorrhage was treated by ligation of both ends of the severed bleeding vessel. Enlargement of the wound was accomplished parallel to the long axis of the neck to avoid injuring important nerves or blood vessels[2].

It was known that if one carotid artery were ligated, cerebral disturbance occurred in one-fifth of the cases and in half of these (one-tenth of cases) the outcome was fatal. When both carotids were ligated simultaneously, death always ensued. If the two carotids were ligated several days or weeks apart, there was no greater incidence of cerebral disturbance than when one carotid alone was tied.

Hospitals in the Confederate States. Richmond became a vast collection of hospitals during the war just as did Washington and Alexandria in the North. There were twenty-seven numbered hospitals in Richmond, and over fifteen named hospitals.

Many of the casualties were nursed in private homes by the ladies of the Confederacy. The total amount of care rendered or the number of cases treated will never be known. Not only were the wounds of the Confederate soldiers cared for, *but* their wants in clothing and food were satisfied as well. "A soldier taken into a private home often went forth after his convalescence wearing a beautifully patched uniform and underwear made from the linen of the women, who sacrificed their own clothes and comfort for the benefit of the men at the front." [5] Numerous female philanthropists aided the Southern hospital cause. In Nashville, Mrs. Felician Grundy Porter worked unceasingly to establish hospitals for the wounded. As president of the Women's Relief Society of the Confederate States, she arranged concerts and tableaux and so collected vast sums of money for the purpose of establishing hospitals and buying artificial limbs for Confederate amputees[5].

Another heroic Confederate woman was Sally B. Tompkins, who expended most of her ample resources establishing and maintaining the Robertson Hospital in Richmond. This hospital was operated with a high degree of efficiency and established an enviable record, admitting 1333 patients of whom only 73 died. Soon after the war began, an executive order was issued which placed all private hospitals under Government control. Because it was feared that such an order would cause the Robertson Hospital to lose its benefactor, President Davis commissioned Miss Sally B. Tompkins a captain in the Confederate States Army. Sally Tompkins accepted this commission, but refused to place herself upon the payroll of the Confederate States. The commission given to Captain Tompkins was the *only one* granted to a woman by the Confederate States Army.

The most famous Confederate hospital was the Chimboraza Hospital of Richmond, with 8400 beds. During its three years of operation, it treated 76,000 patients, of whom 17,000 were battle casualties, with an over-all mortality of approximately 9 per cent. Shortly after the first battle of Bull Run, before the Peninsular Campaign, the Surgeon-General commissioned Dr. James Brown McCaw, of Richmond, to establish and direct this hospital. Still in his thirties, McCaw already

had been editor of the Virginia Medical and Surgical Journal for years, and was professor of chemistry and pharmacology at the Medical College of Virginia. McCaw organized his huge hospital into five divisions according to states. This hospital encompassed 150 buildings and 100 Sibley tents (of the tepee type). McCaw showed his genius for administration by buying several large tobacco warehouses in near proximity to the hospital, which he utilized for the manufacture of soap. The well-seasoned lumber used for tobacco boxes, obtained by this purchase, was utilized to build bedsteads, furnishings, and partitions. McCaw used the factory hands for manual labor. Further construction included large icehouses, a Russian bathhouse, a sewage disposal unit, and a bakery. Water wells were dug. A brewery was established with a capacity of 400 kegs of beer to a brew. McCaw maintained large herds of cows and goats, and to procure fresh vegetables, several canal boats plied the James River Valley purchasing fresh vegetables for the patients. The total staff numbered 120, of whom 40 to 50 comprised the medical staff.

During this period of intense activity, McCaw found time to serve as editor of the "Confederate States Medical and Surgical Journal", and within the fourteen numbers of the journal, six scientific reports appeared from the staff of his own Chimboraza Hospital.

Benefits for Confederate Veterans Following the War Between the States. Following the war, most of the Confederate States recognized their obligation to assist the disabled and destitute war veterans, and the most generous states, which led in veterans' services, were Louisiana, Georgia, Florida, and Virginia. Considerable sums of money were appropriated to furnish artificial limbs to indigent amputees. In 1866, the state of Georgia appropriated $30,000 for this purpose, and $20,000 was appropriated by the Florida legislature in 1886. A pay scale for disability considered generous at that time (the state of Florida) consisted of annual payments of $150 for loss of sight or of both hands or feet, $30 for loss of one eye or loss of hearing. Artificial legs costing about $80 were purchased for amputees, and $25 was provided for repair of a prosthetic extremity.

This, then, is a short chronicle of a small valiant corps that labored, though unprepared and undersupplied, to aid 3,000,000 sick and wounded in the last of the romantic wars in which the individual was yet a major factor. Individual performances ranked high, and the figures

of mortality and morbidity compared favorably with those of the adversary. In lieu of official documents, however, the final history of the Medical Corps of the Confederate States Army must wait to be written when personal documents are released by families to the great libraries. Then more able scholars than we will make their appraisals.

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ANNUAL BIBLIOGRAPHY OF MEDICAL REVIEWS

Volume 3 in this series will be published by the National Library of Medicine in June 1958 and will be available from the *Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.,* at a price presently estimated at $1.25.

This volume is arranged by subject with a separate author index and will list approximately 2900 references to review articles in clinical and experimental medicine and allied fields which have appeared, largely in 1957, in all of the current journals received by the National Library of Medicine.

HUMAN BLOOD IN NEW YORK CITY*

Report of a Study of Its Procurement, Distribution and Utilization†

Summary of Findings and Recommendations

"Disunity, disorganization and disorder" characterize the overall picture of the activities by which New Yorkers are provided with blood and its derivatives to be used in the treatment of disease and injury, according to the report of a survey of 158 agencies that engage in some or all phases of providing blood.

Taking as its main thesis the position that the provision of blood is a community concern, the report asserts that the individual agencies performing this service "are not gauging their thinking on a community scale or visualizing their role in the larger situation; nor are they working together with mutual trust." Furthermore, their practices as revealed by the survey "betray a mutual disregard, lack of confidence and even competition", the report continues.

The survey was carried out by the Committee on Public Health of The New York Academy of Medicine at the request of representatives of the blood-handling agencies themselves. According to the report, the agencies had become increasingly aware of growing problems, and in order to bring about improvement, factual data on the whole situation were needed.

Throughout the report the principal recurring theme is existing variation—in policies, practices and technical procedures. Repeatedly, the tabulated data show that the blood agencies are operating with no suggestion of uniformity. In the face of this condition, the report presents sixty detailed recommendations centered around a proposed coordinating agency, which would establish cooperative and advisory relationships with all the operating blood banks in the city.

"If the blood agencies agree to work together toward a common goal, the good of the whole community, and if they join together in establishing a system with adoption of the same practices and standards of operation, they will create a climate of cooperation, mutual respect, and trust. By orienting their individual interests toward the larger objective, they will conduct their operations with community-mindedness", the Committee's report declares.

To achieve the objective of a service dedicated to the public welfare the Committee recommends first, that all the blood-handling agencies in New York City formally organize, on a permanent basis, a community body concerned with blood.

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* Published by The New York Academy of Medicine, April 21, 1958.

† The Study was conducted by a Subcommittee of the Committee on Public Health of The New York Academy of Medicine. The membership of this Subcommittee included: Dr. Milton J. Goodfriend, Chairman; Drs. Henry Aranow, Jr., Alvan L. Barach, Linn J. Boyd, L. Whittington Gorham, Harry Most and Howard A. Patterson, members. Dr. Harry D. Kruse, Executive Secretary of the Committee on Public Health of The New York Academy of Medicine, served as General Director.

The aims outlined for the central agency include: planning on a community level, improvement in standards of operation, standardization of procedures and technical methods, encouragement of research, and improvement of relations with the public.

From the recommendation of a central agency flow all the remaining recommendations, which set forth in specific details the duties of every participant in the proposed community organization.

The central agency would have administrative, advisory and planning functions related to all phases of blood-handling. Its first recommended action would be to set up a community blood center, which would carry out the administrative duties, assist the member organizations, and meet supplementally the community's needs for blood.

Among the specific tasks which such a center would undertake would be:

Ascertain the community's need for blood and the potential supply.
Maintain an inventory of all blood in the city, and central records of its use.
Promote and assist in the recruitment of donors for all agencies.
Handle emergencies and inter-agency transactions, such as providing rare types of blood and distributing temporary over-supply, transferring blood from one agency to another if needed.
Establish a bureau for complaints.
Foster and engage in research.

The Committee came to the conclusion that New York City depended too much on paid donors, in view of the fact that 42 per cent of all blood was obtained from this source, whereas elsewhere in the United States as a whole, the percentage was only 2 per cent from paid donors. The report states: "It is clear that if the use of professional donors is diminished, the public will have to play a larger part in providing blood. . . . The public must be made to realize that the provision of blood at regular intervals, not just in emergencies, is a responsibility and a civic duty if the city is to maintain a supply of this life-saving product."

Among the glaring deficiencies revealed by the survey is the inadequate keeping of records, and the wide variation in such systems as are maintained, the report states. To bring about improvement in records, without which the proposed blood center could not carry out its function of coordination and community planning, the survey committee makes explicit recommendations for standardized records and names the development of an efficient system as one of the Center's principal responsibilities.

The Committee makes strong recommendations on two aspects of the blood situation that are said to have caused mystification and irritation to the public.

One of these is the variety of replacement ratios. Requirements for replacement of blood used for the sick or injured run from a pint-for-pint arrangement or two or three pints for one pint, the data show. The report urges that standard ratios be set for replacements of blood by friends and relatives of patients, and similarly, that standard exchange and credit systems be established.

The second problem arises from charges for blood, which are equally inconsistent from one institution to another. "The survey has shown an altogether astonishing variability in schedules of charges in different institutions", the report states.

Total charges for the first transfusion ranged from $14 to $51 in voluntary hospitals and from $25 to $60 in proprietary hospitals.

The Committee has several suggestions for improvement in the matter of charges. In its opinion, blood should not be sold for profit. "This means," the report explains, "that a hospital's transactions in blood should not be profit-making; the blood delivered to the patient should be priced accordingly. Thus, any profit resulting from the handling of blood should indicate an opportunity for lowering the price of transfusions, not for diverting the profit to another department of the hospital which is not breaking even, or for assigning the extra income to general funds."

Recognizing that voluntary and proprietary hospitals have different overhead expenses, the Committee urges that each group analyze its costs and attempt to set fixed prices to be charged to patients. The prices in the two types of hospitals would probably not be the same, but the Committee recommends that there be "a ceiling on the price of provision of blood throughout the city in each type of institution", and emphasizes that any difference in the price ceiling should be well-founded and fair.

The Committee also makes a strong plea for the abandonment of a deeply intrenched practice —charges for blood varied according to the type of accommodation in the hospital; that is, ward, semiprivate and private. "The Committee believes that this practice violates the very principle of providing blood without profit", the report declares.

The Committee's recommendations on charges and billing were as follows:

> "Develop a standard system of charges for blood and the services incident to transfusion and set a maximum charge.
>
> "Formulate a uniform system of billing patients to supplant the present confusing multiple systems."

The recommendations spell out in detail the points in which the Committee believes the collecting and distributing agencies can improve their own operations and thus contribute to the community's welfare. They emphasize recruitment of donors, record-keeping, uniform processing of blood, investigation of transfusion reactions, and study of the economics of production so as to arrive at uniform charges for processed blood.

Hospitals, as the chief users of blood and blood derivatives, are urged to adapt their policies, practices, techniques and record-keeping systems to those devised and recommended by the proposed central agency. Specific recommendations concern problems which are peculiar to the hospitals, including facilities for storage and transportation, pretransfusion examination of patients, uniform and standard cross-matching tests for the blood; records of transfusion reactions and study of such reactions by the clinical pathologist of the hospital and by the community blood center; the provision of adequate technical staff on nights, week-ends and holidays, and the wastage of blood. These recommendations are in addition to those on charges and billing, which affect the hospitals most deeply.

The formal request for the survey was presented in March 1956 to the Academy of Medicine by an *ad hoc* committee representing twelve interested organizations, with Dr. August H. Groeschel, Associate Director of The New York Hospital, as chairman. The director of the survey was Dr. H. D. Kruse, Executive

Secretary of the Academy's Committee on Public Health. The work was guided by a subcommittee under the chairmanship of Dr. Milton J. Goodfriend.

The major objectives of the study as stated in the report were: "1) to obtain factual data concerning the policies, practices, procedures, volume handled, facilities, equipment, replacement ratios, charges, and other information related to procuring, processing, preserving, using, and exchanging or selling whole human blood and blood derivatives in New York City; 2) to identify the problems that must be solved in order to establish better practices and to obtain improved results in dealing with whole human blood and blood derivatives; and 3) to recommend the action that should be taken to place blood-handling activities in New York City on a sound basis in terms of community needs."

The study consumed eleven months, during which information was collected from the 158 blood-handling organizations by means of questionnaires and in more than half the instances, by actual visits. Of all the establishments engaged in blood activities in New York City, only two, under the same ownership, did not participate.

The problems that enter into blood-handling in New York City, as identified by this exhaustive study, were the following: lack of community interest, the perishable nature of blood, differences in policy, public misunderstanding, lack of a coordinating agency, uncoordinated planning, incomplete and nonuniform records, lack of standardized processing methods, personnel shortage, and limited facilities.

DATA ON INTERNATIONAL CONGRESSES REQUESTED BY LIBRARY

FELLOWS are reminded that the Library is eager to acquire the publications of all international congresses, their programs, bulletins, proceedings, reports. Since these are often hard to find, it would help a great deal if Fellows attending such congresses would turn over to the Library any such papers as they themselves do not wish to keep. Such thoughtfulness would be deeply appreciated.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting of May 23, 1957, at The New York Academy of Medicine

An Investigation of the Relation between Immediate and Delayed Hypersensitivity as Illustrated by Local Lesions in Rabbits

PHILIP G. H. GELL

Department of Pathology, University of Birmingham, England

Study of the types of cells specifically involved in hypersensitivity reactions can give some insight into the mechanism of their causation and development, and throw light upon two problems: first, what is the "sensitized" cell in delayed sensitivity, and secondly, is there any direct continuity between the cell that takes up antigen, the cell that becomes "sensitized", and the cell that produces and secretes antibody?

It is first necessary to consider the "architecture" of the various sorts of hypersensitivity lesions and the changes in such lesions with time. In a study of various sorts of lesions produced by intradermal injections in rabbits, Gell and Hinde[1] attempted to isolate certain reaction-patterns which could be recognized in complex lesions. These were: 1) the vasculo-necrotic pattern, best recognizable in the passive Arthus reaction at 24 hours, which consists essentially of thrombosis of the small venules with platelets and white cells, leading to acute necrosis and massive invasion with polymorphonuclear leukocytes; 2) the "perivascular-island" pattern, best seen in a mild tuberculin reaction at 24 hours, but persisting in such sites for days or weeks, consisting of the "cuffing" of the small vessels with mononuclear cells, without any gross damage to the circulation or vessel; this picture is, however, identical with that seen in a mild Arthus reaction at three to four days, when the polymorphonuclear exudate has cleared; and 3) the "plasma-cell transformation" which occurs in Arthus reactions after five days and consists of the progressive transformation of the mononuclear cells to pyronin-positive cells and finally to typical plasma cells. The attempt was then made to follow the development of Arthus-type sensitivity histologically. Intradermal injections of full antigen (human gamma globulin) were made thrice weekly in rabbits and the lesions so produced examined macro- and microscopically. Microscopic examination of lesions at 24 hours showed that the first cell to appear as sensitivity developed was the mononuclear; by about the sixth injection, a pure perivascular island picture was produced indistinguishable from a "tuberculin" reaction. In subsequent lesions a central polymorphonuclear exudation, with vascular damage, became more and more evident, until finally this predominated, leaving only a peripheral zone of mononuclear reaction; it became, in fact, a typical active Arthus reaction. This suggested that the active Arthus reaction is a "vasculo-necrotic" type of reaction imposed

upon a "perivascular island" pattern of tuberculin type. Passive reactions produced by transfer to normal animals of serum or of blood cells, separately, showed that serum-sensitized animals tested intradermally with antigen showed an intense vasculonecrotic phase, while the "mononuclear" phase (best seen in active reactions at the third day) was inconsiderable; while cell-sensitized recipients showed a rather weak primary reaction, but a mononuclear reaction at three days which was disproportionately intense.

Experiments are being carried out in an attempt to identify the "sensitized" cell that enters the lesion, and to confirm the observation that such a cell matures to a cell resembling a plasma cell, by the injection of carbon particles before and after the establishment of various sorts of lesions. In general, it has been found that in an animal which has phagocytosed carbon and is then treated with antigen, a certain number of carbon-containing macrophages find their way into the lesion, presumably from spleen or bone marrow. If, however, carbon is injected into an animal as the lesion is appearing, the endothelial cells of the small venules become heavily loaded in their cytoplasm, and carbon-containing cells move out with the perivascular infiltrate in large numbers. The possibility is suggested that this is actually the result of proliferation of vascular-endothelial cells, rather than of the perivascular adventitial histiocytes, as is usually believed, and that vascular endothelium may be one specifically "sensitized" tissue. In the plasma-cell reaction in the late Arthus lesion, in carbon-injected animals, carbon may occasionally be found in mature plasma cells, suggesting that they have developed from macrophagic cells, but such experiments are still incomplete. As a working hypothesis, it is suggested that the cell that takes up antigen in small amounts may become "sensitized" and capable of taking part in a "delayed" reaction (though such a reactivity in Arthus-sensitized animals is usually suppressed by the vasculonecrotic phase): this "sensitized" cell when in the tissues and in the presence of retained antigen may then mature to an antibody-producing plasma cell.

DISCUSSION

MERRILL W. CHASE: We have heard tonight the net result of a broad area of research in which Isobel Hinde and our speaker have been engaged for so long, one in which the cellular reactions occurring within test sites on rabbits have been carefully quantitated by study of section after section; it represents a necessary pattern of work to which so few people are willing to devote the required amount of time and carefulness. From a fairly complex series of changes within the tissues, there have been sorted out certain patterns that are associated with Arthus-type reactions and with tuberculin-type reactions respectively; one pattern or the other can be discerned in rabbit lesions, and sometimes the participation of both simultaneously.

It seems to this discussor, whose work with drug allergy in guinea pigs has led him to differentiate more sharply between the two types of reactions (immediate and delayed) than Dr. Gell does, that the rabbit may not be an advantageous species for studying and differentiating between the varieties of tissue response. In this species, reactivity towards tuberculin after the sensitization is not especially high, old tuberculin in dilution of 1:5 to 1:100 being frequently required, whereas the Arthus-reactivity of the rabbit and its related concentration of circulating antibody are generally more pronounced than in other species. In consequence, a "ratio" of delayed to immediate hypersensitivities (expressive of the rabbit's capacity to exhibit the two effects) could be represented as a fraction having a small numerator and a large denominator. The reverse of this may describe the ratio of delayed to immediate hypersensitivities in the guinea pig, possibly even best with respect to sensitization with drugs: the delayed component is high, antibody production is low. Our points of view, therefore, may be conditioned by the evidence that has been available to us. From my own experience, which is based on experimental manipulation and not on histologic observation, I conclude that the delayed-type of drug allergy in the guinea pig is distinctive and differentiable from reactions of the "immediate" type, that is,

reactions referable to the classical types of circulating antibody.

For example, in certain specific test sites made on guinea pigs that have been appropriately sensitized, one can distinguish the co-participation of Arthus-type and delayed-type responses at the same site; further, by specific desensitization one can suppress or abolish the capacity to give Arthus-type reactions and leave the delayed-type of reactivity essentially unimpaired.

The studies which Dr. Gell presents are, therefore, paralleled in certain guinea pigs sensitized appropriately with selected chemical allergens, in that we can find either pattern occurring alone or both appearing together with some degree of linkage between the two.

One particular result that we have seen in the guinea pig merits specific reference, not because it contradicts but because it may be explained on the basis of Dr. Gell's observations with rabbits, with respect to his findings of vascular cuffing following a local test. When a guinea pig has been rendered hypersensitive to tuberculin, and a tuberculin test of moderate intensity has been made on the belly wall by means of the tuberculin preparation PPD, the animal exhibits the typical, delayed-type of reaction to tuberculin and the site then slowly reverts and approximates its normal state. (The intensity of the test has been arranged so as to avoid local sloughing, but to exhibit the characteristic shift from brawny edema at 24 hours to induration at 48 hours—characteristics that lead us to recognize this reaction as being a typical tuberculin reaction.) After recovery of the site, say three weeks later, 25 gamma of PPD are injected subcutaneously at a remote site. There ensues around these former test sites, commencing within some hours and reaching a maximum within 24 hours, a specific reaction that reveals the existence of a local immunologic alteration at these sites. This would fit very well with Dr. Gell's statement that monocytes persist for some time in a perivascular location at the site of tuberculin reactions conducted in the rabbit. Yet the new reaction is probably an anti-protein reaction, and not a delayed type of reaction. If my statement as to the sequence and interpretation of events is correct, the animal that has been caused to undergo a reaction of delayed type acquires at a test site not only what Inderbitzen[2, 3] has reported—an increased amount of histamine, detectable for several days and attributed to the ingress of cells—but also an immunologic activation, likewise probably owing to the localization of wandering cells, which appear to become engaged in antibody formation. When the tuberculin preparation PPD is supplied later in moderately high concentration at a remote point, it appears to reach the locally altered former test site and to induce there a reaction which is not a delayed type of reaction. My illustration should underline the complexity of the events as they occur *in vivo*. Decipherment of the component parts will not be an easy task.

I should like to point out still another situation which emphasizes some of the difficulties in interpreting, classifying, and understanding types of reactions. Dr. Janet McCarter, working at the University of Wisconsin, studied tuberculin tests in students. When it fell to her lot to use the first preparation of avian tuberculin that had been made with use of only minimal heating, followed by mild concentration on the ultrafilter, it was found that students who were negative in her initial test series responded transiently to later re-testing. The new type of preparation actually was antigenic. On the average, the maximum reaction occurred at 24 hours; some of the reactions persisted through the second day and would have been judged tuberculin-positive if observed only at that time. We are not required to accept the "positive" reactions, observed in re-testing, as being a delayed type of reaction, but we are obliged to recognize that the need to use minimal test strengths of tuberculin (in order to avoid focal and systemic reactions in highly sensitive individuals) and the bother of making step-wise tests on a patient often cause us to stop short of any critical appraisal of the types of skin reaction that we encounter in human skin-testing. When a reaction persists for a sufficient length of time for us to recognize it as positive we are likely to interpret it as a delayed type of reaction.

Dr. Gell has attempted to sort out the types of reactions on a histologic-biologic basis. Attempts of this sort must be pursued eventually with species other than the rabbit before all the necessary data come to hand. We are indebted to, and must congratulate Dr. Gell on the foresight that led to the work summarized here tonight.

A. R. MILLER, Seattle, Washington: If I understood correctly, Dr. Chase stated that monocytes become antibody-producing cells.

MERRILL W. CHASE: No, I did not intend to describe it so baldly; the cellular events in the perivascular area are probably complex indeed.

A. R. MILLER: I am wondering if it has to be a monocyte, or the cell which surrounds the antigen has to be the cell that will entertain the antigen and also would have to be the cell that produces the antibody. In other words, could it be a cell of a particular sort, such as the cell of the 8th nucleus of the pons that would take over the antigen-antibody reacting mechanism? I understood Dr. Chase to say that the cell became the antibody-producing agent, that the antigen itself, the PPD, was not the antigen in this reaction, so it seems to me the only way we could desensitize an individual would be in some way to extract the cells, make up an antigen of that, and desensitize to the cell itself.

MERRILL W. CHASE: The production of antibody is related to both splenic and non-splenic sources, and, as has been shown by Oakley, Batty and Warrack in England[4, 5] and by others in this country, one can have local concentrations of antibody in different tissues; hence we can assume a local concentration of antibody in a node on one side of an animal and its practical absence contralaterally. The types of cells that are engaged in producing antibody are not precisely known, but it is generally regarded as a function of the pre-plasma cell. In my own opinion, the lymphocyte is at least part of an alternate parallel pathway. The lymphocyte does not necessarily play a complete role; possibly it provides some necessary material to other types of cells. This does not bear on anything that I have said, and I think it was Dr. Gell and not I who talked about plasma cells arising in such areas, in which there were concentrations of plasma cells and monocytes.

A. R. MILLER: I would like to ask Dr. Gell the same question.

PHILIP G. H. GELL: I am not sure that I understand it; will you please repeat your question?

A. R. MILLER: Let us take the 8th nucleus of the pons. Say we have a concentration of plasma cells around the vessels in this nucleus. Could it be possible that the nuclear cells themselves would take over the antigen, and also by retaining antigen itself produce antibody? In other words, your plasma cells and lymphocytes are left out of the picture.

PHILIP G. H. GELL: I do not think there is any conclusive evidence one way or the other at the moment; it is possible that a small amount of antibody or a small amount of gamma globulin may be capable of being produced in any cell in the body—it is certain only that the bulk of the antibody is produced in cells of the lymphoreticular system.

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Homotransplantation of Human Cell Lines

(Abstract)

CHESTER M. SOUTHAM

Sloan-Kettering Institute for Cancer Research

The growth of established human cell lines after subcutaneous homotransplantation into healthy adult male volunteers and volunteers with advanced debilitating neoplastic disease has been studied[1]. The subcutaneous nodules which appeared at the inoculation sites were biopsied at various intervals from one week to eight weeks after implantation. Histologic findings were illustrated by lantern slides. Data illustrating the following observations and conclusions were presented.

Behavior of a given cell line on homotransplantation appears to be independent of its site of cultivation. For example, HEp #3 cells grown in tissue culture, egg chorioallantoic membrane, or cortisone-treated rats, mice, or hamsters have shown no apparent differences attributable to source.

Normal recipients have rejected implanted cells of all types. Regression is usually complete by three weeks, and some biopsies taken as early as seven days after implantation show no evidence of propagation or persistence of the implanted cells. Rejection in normal recipients was characterized, grossly and microscopically, by an acute localized inflammatory reaction at the implant site. Polymorphonuclear leukocytes were prominent in this reaction, but mononuclear cells including plasma cells were also present in large numbers, and eosinophiles were prominent in some specimens.

In the cancer patients rejection was delayed or did not occur at all during the period of observation. Acute inflammatory changes were minimal and transient or did not occur at all. Growth of the implanted cell (all cell types) was demonstrated in 20 of the 22 patients studied to date. Growth continued for two weeks or longer before there was regression in any of these patients, and in three individuals there was still active growth of the implanted cells at six weeks or later. When regression did occur it was characterized by degenerative changes of the implanted cells and a mononuclear cell infiltration with little or no polymorphonuclear response. If there was no spontaneous regression the study was terminated by complete excision of the implant or by expiration of the patients due to their own advanced cancer.

The several cell lines showed consistent differences in growth potential within both of the two categories of recipients (cancer patients and normals). Normal fibroblasts never gave any detectable evidence of propagation. Chang's conjunctival cells (epithelial cells of normal origin but showing hyperploidy and other cytologic abnormalities) never grew in normal recipients and grew slowly in the cancer patients. Most of the neoplastic cell lines (HEp #1, HEp #2, HeLa, J-111, and HS #1) formed a group which appeared to have about equal growth capacity. In normal recipients these cells were found in almost all biopsies taken on day 7, although they usually showed considerable cellular degeneration and were enmeshed in acute inflammatory tissue. In the biopsies taken on day 14 they were still demonstrable in somewhat less than half of the recipients. In the cancer patients these cells produced nodules of healthy-appearing cells in almost all recipients in the biopsies taken at two weeks or later after implantation, and in a few cases growth was progressive for three to eight weeks. The HEp #3 cell is in a group by itself. It was the most vigorous and aggressive of the cell types studied as judged by behavior in both groups of recipients. In

normal recipients all biopsies taken on day 7 contained HEp #3 cells although there was also a vigorous inflammatory reaction. About two-thirds of the biopsies taken on day 14 contained identifiable HEp #3 cells, although usually degenerative changes were prominent. In one normal recipient a nodule was still growing and contained cancer cells 21 days after inoculation. In the cancer patients growth of HEp #3 cell implants recurred three times after excisional biopsies and grew progressively in these three patients for six weeks or longer (that is until the patient died of the primary disease). In one of these individuals there was metastasis from the inoculation site on the forearm to the axillary nodes. In the other two cancer patients who received HEp #3 cell inoculation, one showed no recurrence after excisional biopsies on day 19 and the other died of his primary disease seven days after implantation.

In attempting to determine the cause of the difference in reaction between these two groups of recipients, an attempt is being made to investigate cellular and humoral defense mechanisms of all known types. Time does not permit a detailed discussion and these studies are still incomplete, but it may be stated that there appears to be no inability of the cancer patients to produce an acute inflammatory response to other types of stimuli and no defect in their ability to produce circulating antibodies against viral antigens. An interesting observation in the cancer group is the frequent occurrence of very low properdin levels. In the data accumulated to date there is a direct correlation between serum properdin levels and the observed regression of implants. However, there is neither evidence nor implication that this relationship is causal, and the possibility that there may be a relationship between properdin and transplant rejection has not yet been subjected to critical investigation.

The growth of a repeat implant of the same cell type has been studied in normal recipients. The repeated implants formed smaller nodules and regressed more rapidly as judged by gross and microscopic examination. This accelerated rejection of a second implant is presumably the result of an induced immunity. It has not yet been possible to study this phenomenon in patients with advanced cancer.

All of these studies concern only homotransplanted cells. There is no implication in our results or any of the statements concerning them that these observations have any carry-over to spontaneous cancer.

REFERENCE

1. These studies have been possible only because of the cooperation and collaboration of many physicians, laboratory scientists and technicians, and volunteer recipients, at Memorial Cancer Center, Ohio State University, and Ohio State Penitentiary. The speaker acknowledges his indebtedness to these many co-workers. A preliminary report on some of these studies has been published: Southam, C. M., Moore, A. E. and Rhoads, C. P. Homotransplantation of human cell lines, *Science 125:* 158-60, 1957.

DISCUSSION

HARRY S. N. GREENE, New Haven, Conn. I do not think that Dr. Southam need apologize for entering the domain of homotransplantation. The present extreme confusion in the field is due largely to the fact that people who are neither pathologists nor transplanters have worked so intensively in it.

As I understand it, the primary results of his experiments have been that cultured human cancer lines will not grow in normal individuals, but will grow in cancer patients. The subject of homotransplantation has been intensively studied, using legitimate experimental animals; the findings, which are similar to those cited, have been published and are well recognized. The success of homotransplantation of any tissue depends on two factors: first, the status of the tissue used for transfer, and second, the status of the host used, and this is particularly true in cancer. Cancer is, of course, not a sudden transformation of normal cells, but, on the contrary, represents the final stage in a developmental process. Throughout this process the morphology of the cells may remain completely unchanged, but tl tumor undergoes profound biologic changes, and these are expressed in transplantable reactions. If one divides the development of cancer into its two main phases, first, the phase in which the tumor is not metastasiz-

able, and second, the phase in which it is metastasizable, one gets two radically different sets of transplantation reactions. In the pre-metastasizable phase the tumor will grow when transplanted back elsewhere in the tumor-bearing individual, but it always fails to grow when transplanted to normal individuals, whether the normal individual is of the same species or of a different species. Let me repeat that: A tumor in a pre-metastasizable phase of development will grow when transplanted back elsewhere in a tumor-bearing individual. It always fails to grow when transplanted in a normal individual. In other words, at this stage of development the tumor is dependent for its continued existence and growth on factors peculiar to the tumor-bearing animal. These factors are not supplied by normal animals, and accordingly the tumor will not survive transplantation in normal animals. With continued development the neoplastic focus attains a new property, the ability to metastasize, and coincidently, it attains independence of the factors concerned in its genesis and development. Thus, a metastasizable tumor will grow not only on an autologous transfer, but it will also grow on transfer to normal, unrelated animals, even if the animals are of a different species. Let me emphasize this, using a particular tumor, a spontaneous breast cancer in one strain of my rabbits. It is a very constant tumor, the sequence of morphologic and biologic changes being the same in all cases. It begins as a cystic enlargement of the ducts and acini; over a period of time small foci of neoplasia occur in the dilated cysts and ducts. These always occur just as uniradicular papillomata, and then become multiradicular, and have the complicated structure seen in the present slide. A high power of this slide shows all of the cellular changes generally thought to be characteristic of cancer, that is, a considerable increase in the number of mitoses, loss of polarity, and marked irregularity in nuclear size and staining qualities. But for a considerable period of time the tumors remain confined within normal boundaries, and do not invade. If one obtains a biopsy at this stage of development and transplants fragments in the anterior chamber of the eye of normal rabbits, the transplants fail to take. This is a section of such a transplant three weeks after transplantation, — obviously dead. However, if fragments obtained from the same biopsy specimen are transferred to rabbits bearing spontaneous breast tumors the transplants survive and grow. In this stage of development the tumor is dependent for its existence on factors peculiar to the tumor-bearing host, and these factors are not supplied by the normal animal. With continued growth the primary tumor attains the ability to invade and metastasize, and if one transplants a fragment of tissue obtained at this stage one finds it will grow in normal animals. Not only does it grow in normal rabbits, but it grows in animals of any species, and the next slide shows the same tumor growing in the anterior chamber of the eye of a guinea pig. Thus when a tumor attains the metastasizable phase of development, it also attains independence of the factors it originally depended on, and will grow in their absence. This is not only true of tumors of rabbits, it is true of all cancers, whether in animals or man.

This slide shows the situation in a spontaneous carcinoma of a C_3H mouse. A biopsy was performed on that tumor in March of one year. Fragments of the tumor grew on transfer to other C_3H mice, but failed to grow in foreign mouse strains or in an alien species. The tumor was biopsied again a month later, and again fragments grew on autologous transfer, but not on homologous or heterologous transfer. When the animal was killed at the end of another month, small metastases were found in the lung. Transfer of the primary tumor was performed as in the previous experiments, but this time it grew on heterologous and homologous transfer, as well as in animals of the strain of origin. Thus the transplantation reactions of a tumor are entirely different in different developmental phases, and it is absolutely essential in any transplantation experiment involving cancer to characterize the inoculum. This point concerns human, as well as tumors of other species. The significance of heterologous transplantation and homologous transplantation is exactly the same, and in working with human tumors it is not necessary to use man as an experi-

mental animal. Let me illustrate this point. This slide shows the results of heterologous transfer of a series of 123 different human cancers obtained from the operating room. The tumors were all cancers morphologically. Most of them were carcinomas; there were a few sarcomas. Sixty-five grew in guinea pigs, and 58 failed to grow. In the group of tumors that were heterologously transplantable 64 of the patients are now dead; only one is alive, and this individual is moribund with metastases. Obviously these transfers were performed from patients in the terminal phase of the disease, and the subsequent rapidly fatal course of the patients indicates that in all probability their tumors had reached the metastasizable phase at the time of operation. On the other hand, in the group of patients with non-heterologously transplantable tumors only 12 have died and 46 are still alive and free of tumor. It would appear therefore that in this group the tumors had not attained metastasizability at the time of operation.

My point then is that the transplantability of human cancer depends on two factors: first, the status of the tumor tissue used, whether it is from a metastasizable cancer or a non-metastasizable tumor, and secondly, the status of the patient: whether normal or tumor-bearing. It would seem to me therefore imperative that in the work that has just been reported that the status of the tumor used be clarified.

I should also like to raise the point as to the necessity of using human beings in such an experiment as this. In some backwoods district of New England, remote from the sophisticated institutions of this City, we still believe in the dignity of man. That belief may be an illusion, and probably it is, but it is an illusion that surely should be preserved and fostered.

MERRILL W. CHASE: It seems to me that what we have heard tonight, if I interpreted it aright, is this: most of the materials with which Dr. Southam has been working have not been of the metastasizable sort, for they either were not effective as "takes" when supplied to normal individuals or they regressed rapidly. Speaking of these experiments as an immunologist, I wonder whether one cannot view them in this wise. Does Dr. Southam not have here a situation of immunologic tolerance in cancerous individuals to some class of antigens that is indigenous to cancerous cells, and of absence of tolerance (i.e., rejection) in normal individuals? Obviously we cannot picture simply the antigens of normal cells as meeting the needs of our hypothesis, because we have been told that normal fibroblasts are rejected by both classes of recipients. If we are going to pursue this line of reasoning, these antigens should be something special and common to an entire series of cancerous cells, and indeed many of the cell lines used were epidermoid in origin. Could these cancerous cells possess some special antigen or class of antigens, other than those present in normal cells? Could one picture some sort of immunologic tolerance in cancer patients, possibly connected with a high metabolic rate of the cancerous tissue, a liberation of certain antigen materials (nuclear in origin? present in the native state or as split products?) and a saturation of the chief antibody-producing sites?

If this were the case, possibly a kind of immunologic tolerance could be set up. A pertinent model would perhaps be the deviation of the usual event of isoallergic encephalomyelitis by special prior injections of brain tissue, now being studied by Dr. Philip Y. Paterson. Perhaps one could imagine, further, that the antigens involved in Dr. Southam's cell lines are only weak isoantigens, and that some engrafted kind of tolerance against this particular material might be established without too much difficulty. Reasons for the occurrence of such a special antigen or antigens in these cells would be beyond the scope of the hypothesis. One would have, rather, to seize upon Dr. Greene's experiences and his findings that cancerous cells undergo alteration with a maturing process and acquire special new properties of metastasizability. Indeed, it is well known that changes in ploidy occur in many of the cell lines that are maintained under artificial conditions.

It would be pertinent to inquire whether, when an animal has developed an increasing rate of rejection for a given cell line, there is concomitant change in the resistance of

this individual toward other cell lines. Let us rephrase the thought. Would the immunologic experience gained by contact with one human epidermoid cell line condition a person so as to determine his subsequent reaction to all epidermoid cell lines or only to the same epidermoid? Would his initial tolerance for another sort of cell, say a fibroblast, be entirely normal? Answers to these questions might provide some clue in looking for special antigens in cancerous cells. In other words, I would like to have Dr. Southam tell us more about the increase in rejections seen in the non-cancerous subjects.

I should also like to ask Dr. Greene whether he has some explanation for the change he finds to occur in cells that enter the metastasizable phase.

HARRY S. N. GREENE: That to me is the crux of the cancer problem; if the factors distinguishing metastasizable from non-metastasizable cells were known, I think we would be pretty close to the answer. I do not know what the factors are.

CHESTER M. SOUTHAM: Dr. Greene brought up three points that I would like to comment on. First, I would like to ask Dr. Greene if he classifies a specimen as metastasizable or pre-metastasizable on the basis of clinical and histologic characteristics at the time the specimen is obtained and then correlates this classification with its behavior on transplantation. Or, on the other hand, is a specimen classified only after observation of its growth in homologous and heterologous hosts, and then correlated with clinical behavior?

Second, Dr. Greene has suggested that the tumor-bearing animal is more receptive to transplants because the first tumor supplies something which is necessary for the growth of the transplanted tumor, but which is lacking in a normal recipient. In contrast, it has been my premise that the tumor-bearing animal lacks some defensive mechanism which the non-tumor-bearing animal has. While this may be quibbling, since either interpretation provides a useful working hypothesis, these different interpretations are of interest because they might lead to different experimental approaches to the investigation of these phenomena.

Before I discuss philosophical differences across the state border, I would like to consider Dr. Chase's question regarding the increased rejection rate of reimplants of the same or different cell type, and the possible implications of such studies regarding the antigenicity of the several cell types. I did not have time to present our data on repeat homotransplants but my statement concerning the more rapid rejection of second implants was based on two criteria. The first is smaller nodule size. Obviously, nodule size alone is a measure of reactive tissue as well as growth of the implanted cells, but for what it is worth, you see in this graph a plot of nodule size against the number of days after implantation. These studies were all in normal recipients.

In primary implants there was a definite nodule at day 7, maximum nodule diameter at day 14, little further change by day 21, but nearly complete disappearance by day 28. (The data illustrated concerned implants of HEp #2 or HEp #3 cells.) In a group of individuals who were inoculated simultaneously with the primary implant group, but who had received a previous implant of the same cell type some 3 to 4 months earlier, the nodules were at their maximum size at 7 days and were already regressing by day 14. In another group of individuals who had previously received an implant of a different cell type, there was little or no increase in nodule size after day 7, and regression was rapid. The number of individuals in each group is small I know, but that is what we have to work with. From these data I am suggesting the interpretation, but not insisting it is correct, that individuals who receive the same type of cell a second time reject it more rapidly than individuals receiving it for the first time, and that individuals who are having their first experience with a given cell type, but had previously received a different type of cell, may also show an acceleration of rejection, although perhaps not as great as in those who got the same type previously.

One other slide tackles this same question from a different angle. On this chart I

have attempted to quantitate roughly the amount of growth of the implanted cells and the severity of inflammatory reaction. (The data illustrated concerned HEp #3 cell implants only.) At 7 days after implantation all ten biopsies from primary implants contained considerable numbers of the transplanted HEp #3 cells; in the three biopsies from repeat implants of the same cell type, HEp #3 cells were present in only one, and when the HEp #3 cells had been implanted into individuals who had previously received implants of some other cell type, few biopsies (two out of 15) showed as good growth as in the primary implants, three contained no HEp #3 cells, and in the other ten the implanted cells were rare. Similarly in biopsies taken on day 14 most of the primary implants (eight out of 13) contained some HEp #3 cells, whereas in repeat implants of the same cell type the only nodule which had not completely regressed contained no HEp #3 cells, and likewise there were no HEp #3 cells in the two biopsies from recipients who got HEp #3 cells for the first time after previous implants of different cell types.

I am well aware that these data are not adequate to draw conclusions from, but they do suggest the possibility that some antigens are common to the several neoplastic cell types, as Dr. Chase said. I say antigen in quotes, because as yet we have not been able to demonstrate any circulating antibodies. Our only demonstration of an immune state has been this accelerated rejection.

Now to return to Dr. Greene. I think that in general it is fruitless to attempt a rebuttal in philosophical debate, but there are a couple of points here that must not go unchallenged. Dr. Greene—I am not quoting him exactly—is saying in essence that response to heterologous transplantation is not different from response to homologous transplantation and thus (if I am paraphrasing him correctly) we cannot expect to learn anything from the homologous transplantation (which requires human volunteers) which we could not learn from heterologous transplantation in laboratory animals. As a newcomer to the field of transplantation, I am not in a good position to refute this, but neither am I willing to accept it. It has been my assumption that in heterologous transplants the host is faced with tissues which are entirely foreign to it, whereas in homotransplantation some of the antigenic components of the transplanted tissue may be compatible with host antigens and hence might not elicit a rejection reaction. The possibility of continued growth of transplanted tissues has tremendous clinical interest both because of the possibility of using grafts to replace damaged vital structures, and because of the conceivable dangers of introducing into the human body transplanted cells which have neoplastic characteristics or potentialities. These studies of homotransplantation in man have been undertaken in the belief that experimental animal data in general, and results of human cell heterotransplantation studies in particular, could not be applied directly to man, and that the potential clinical importance of homotransplantation justified our request for human volunteers.

But be that as it may, the major point of philosophic difference is Dr. Greene's statement concerning the dignity of man. I would say that the best answer to this would be the attitude of those people who are involved in these experiments as recipients. What do the volunteers themselves think about their personal dignity? I have no idea how many of you have been inside of a prison, but after 16 visits I have come to the conclusion that the inside of a prison is very much like the outside of a prison, and that the individuals there have, at least in their own minds, just as much dignity and just as much individuality as we have here. They do not feel that it is an affront to their dignity, but rather they have demonstrated again and again that they feel it is a big thing which they are doing, or hope that they are doing, for man in participating in this type of work. Maybe some explanation will help. We initiated this project by putting an explanation of the work we wanted to do in the prison newspaper. We stated optimistically that we hoped to get 25 volunteers. Instead, 160 individuals volunteered within a week, and I do not know how many in the next month. There was no other publicity at that time. There was no

pressure or special inducements of any kind. The only reward for doing this was the bolstering of their personal sense of dignity. It is my personal belief that the greatest indignities that man can suffer are sickness and death. This work which we are doing as investigators, and in which these prisoners and patients are participating as volunteers, is predicated on the assumption that we are going to combat these indignities. Whether it will ever actually contribute to improvement in cancer treatment, or any other phase of therapeutics, we cannot even guess, but that is our aim. The idea that the participation of volunteers in such work is offensive to their personal dignity is completely foreign to my own thinking. In fact I feel that such altruistic service to mankind is a convincing demonstration of the dignity of man.

HARRY S. N. GREENE: I will not go further into the discussion of human dignity. Personally I do not feel that the discovery of the cause and cure of human cancer is worth the sacrifice of human dignity attendant on using man as an experimental animal.

The other question that Dr. Southam asked me was about how to determine whether the human tumors to be used were premetastasizable or metastasizable. That of course depends on the physical examination of the patient at the time of operation. If such is not conclusive, then the length of time the patient lives after removal of the tumor is a highly suggestive indication.

CHESTER M. SOUTHAM: You do not mean metastasizable, but metastasizing.

HARRY S. N. GREENE: The terms are probably synonymous.

JOHN G. KIDD: The question could be cleared up by a statement from Dr. Southam as to whether the cells of the growths with which he worked were cultured from growths that had already metastasized.

CHESTER M. SOUTHAM: The HEp #1, #2, and #3 patients are all dead and all had metastatic disease. HEp #1 came in 1953 from an inguinal node metastasis of epidermoid carcinoma primary in the cervix. Death occurred a few weeks after the biopsy was obtained and was due primarily to pelvic cancer causing uremia. HEp #2 was grown from the primary lesion, of an intrinsic larynx carcinoma. Total laryngectomy was performed and recurrence appeared successively in both sides of the neck during the next 15 months and was treated by radical neck dissection. Thereafter the patient had no clinical evidence of cancer. He died of bronchopneumonia at another hospital 27 months after the laryngectomy. At autopsy the only cancer was a metastasis in one adrenal. HEp #3 was grown from the primary lesion of epidermoid cancer of the buccal mucosa which had been diagnosed and treated by x-ray therapy 6 months prior to surgery. At the time the specimen was obtained the disease was recurrent in the cheek and metastatic in the nodes of the right neck at all levels. Postoperatively the disease progressed with extreme rapidity. There was massive pleural effusion positive for neoplastic cells, although chest x-rays were normal one day before operation. Signs of lumbar cord compression appeared and the patient died just two weeks after surgery. No autopsy was permitted.

These three epidermoid carcinomas thus appear to fit Dr. Greene's thesis that those lesions which grow on homo- or heterotransplantation are metastasizing cancers. In contrast, however, are the results with HS #1. This was cultivated from a well-demarcated sarcoma in the left calf muscle, apparently primary in that site. It was signed out as an unclassified sarcoma, possibly a liposarcoma. The only treatment was local excision in January 1953, and there has been no evidence of recurrent or metastatic disease according to the latest chart entry (July 1956). I did not discuss HS #1 very much in my presentation, but you may recall that in one of the cancer patients it grew for 57 days. In the normal recipients it behaved somewhat like HEp #3 although producing less intense inflammation. This tumor then, as well as Chang's conjunctival cells, seems to contradict Dr. Greene's thesis.

May I add, à propos of New England versus New York philosophy, and just for

the record, that I am from Salem, Massachusetts, where our good-intentioned but bigoted forebears hanged the witches.

HARRY S. N. GREENE: We just completed a long series of experiments on the influence of the first transplant on the second, and found there is not actually a resistance to the type of tissue we originally transplanted, but a resistance to transplantation itself.

MERRILL W. CHASE: Dr. Greene's last comment perhaps deals with transplantation into other species, and if so the situation would be different from that of isotransplantation as regards the classes of antigens that would come into prominence. As a basis for our thinking, we might take as a model transfusion accidents occurring during repeated transfusions in which proper account has been taken of the major blood group but not of the existence of minor blood group antigens (M, N, P, Rh, and many others). Reference is made to these erythrocyte antigens because they are well known to us in our daily experiences. Similar or additional antigens occur in sperm cells, in circulating white cells, and in tissue cells generally. Such antigens within fibroblasts are probably the basis for an immunologic reaction that results in rejection of implants of these cells by both cancerous and non-cancerous subjects alike. What then of the inertness of the cancer patient towards human epidermoid cancer cells? There must be an explanation for the presence of a positive anergy that tolerates epidermoid cells but not the antigens of fibroblasts. Such tolerance ought to rest, one would suppose, on some antigen that is dominant in and peculiar to epidermoid cancer cells, being dominant even over antigenic components of normal tissue cells. It would require, also, some degree of related antigenicity between all epidermoid cell lines. The new evidence provided by Dr. Southam suggests that cross-reactions are, indeed, exhibited in view of the suppression that obtains when other epidermoid cell lines are used later on.

Following desensitization the once anaphylactically-sensitized guinea pig can be maintained in the desensitized state providing that we keep supplying enough antigen, for the animal's tissues cannot dispose of the excess antigen. If cancer cells had a property of liberating enough of a special antigen, perhaps a positive "anergy" could be established and maintained in somewhat similar fashion.

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TENTATIVE PROGRAM

EVENING LECTURES – 8:30 P.M.

OCTOBER

13th

STUDIES OF CONTRACTILE PROTEINS OF MUSCLE
Andrew Szent-Gyorgyi, Woods Hole, Mass.

THE METABOLISM OF THE ERYTHROCYTE
Irving M. London, New York City

Subject and Lecturer to be announced

14th

HEREDITARY ASPECTS OF DISEASE
Barton Childs, Baltimore, Md.

CONGENITAL DISEASES OF BLOOD PROTEINS
Charles A. Janeway, Boston, Mass.

HEREDITARY DISEASES OF CONNECTIVE TISSUE
Victor A. McKusick, Baltimore, Md.

15th

SOME MECHANISMS OF BACTERICIDAL CHEMOTHERAPEUTIC AGENTS
Bernard D. Davis, Boston, Mass.

OBSERVATIONS ON THE NATURE OF STAPHYLOCOCCAL INFECTIONS
David E. Rogers, New York City

THE CONTROL OF STAPHYLOCOCCAL SEPSIS
Carl W. Walter, Boston, Mass.

16th

PHYSIOLOGY AND METABOLISM OF THE LIVER
Stanley E. Bradley, New York City

METABOLISM AND CONJUGATION OF BILIRUBIN
Lecturer to be announced

MANAGEMENT OF PORTAL HYPERTENSION
Arthur B. Voorhees, Jr., New York City

(Continued on next page)

17th — THE FATE OF SODIUM AND WATER IN THE RENAL TUBULES
Homer W. Smith, New York City

MECHANISMS OF RENAL TUBULAR TRANSPORT
John V. Taggart, New York City

ELECTRON MICROSCOPY OF THE KIDNEY IN NORMAL AND DISEASED STATES
Johannes A. G. Rhodin, New York City

* * *

PANEL MEETINGS – 3:30 P.M.

OCTOBER

13th — THE DIAGNOSIS AND MANAGEMENT OF CEREBRAL VASCULAR DISEASES
Chairman: Irving S. Wright, New York City

14th — INFLUENZA AND UPPER RESPIRATORY INFECTIONS
Chairman: Walsh McDermott, New York City

15th — GLOMERULONEPHRITIS AND PYELONEPHRITIS
Chairman: William Goldring, New York City

16th — POTASSIUM THERAPY
Chairman: Saul J. Farber, New York City

17th — THE RADIATION HAZARD
Chairman: Joseph E. Rall, Bethesda, Maryland

* * *

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Those who have exhibit material appropriate to the subjects included in the Postgraduate Week program are invited to apply for exhibit space. Forms may be obtained by addressing the Secretary, Postgraduate Week, The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Deadline for receipt of applications, *July 1, 1958.*

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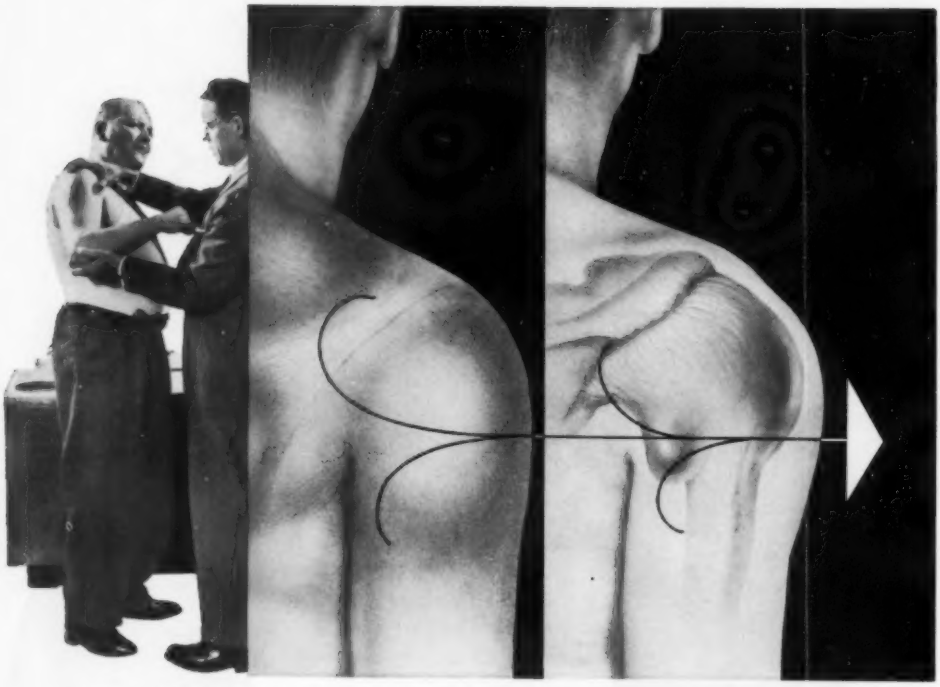

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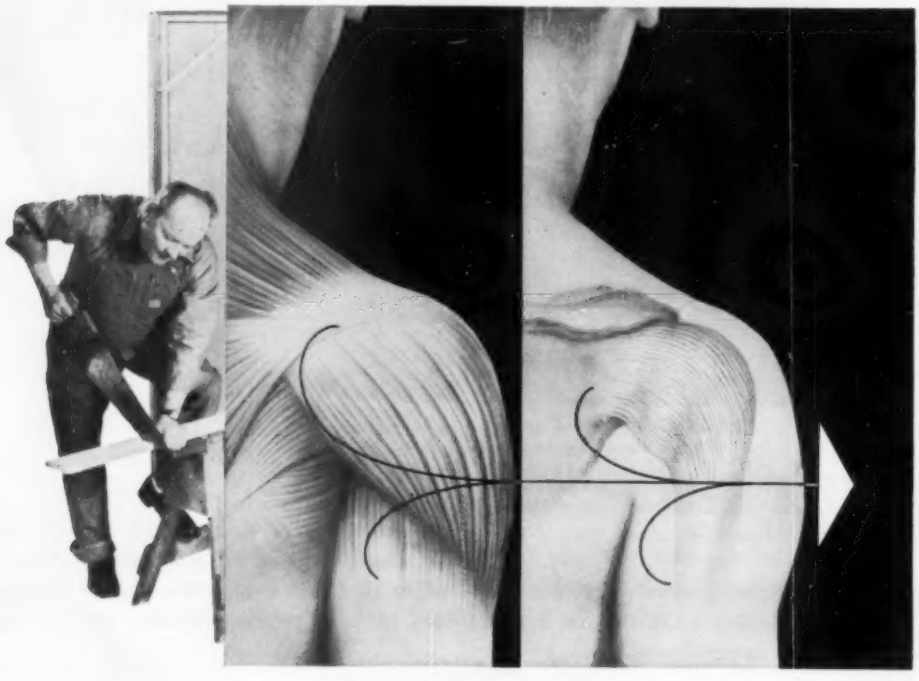

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1. Comroe's Arthritis: Hollander, J. L., p. 149 (Fifth Edition, Lea & Febiger, Philadelphia, Pa. 1953).
2. Merck Manual: Lyght, C. E., p. 1102 (Ninth Edition, Merck & Co., Inc., Rahway, N. J. 1956).

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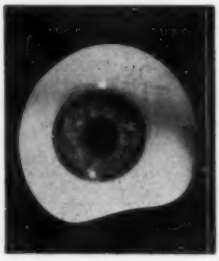

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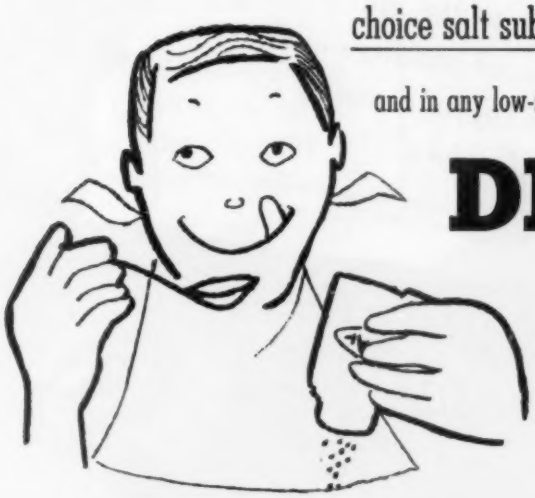

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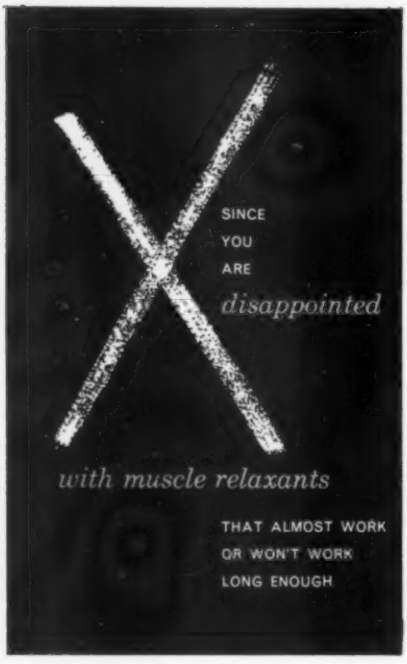

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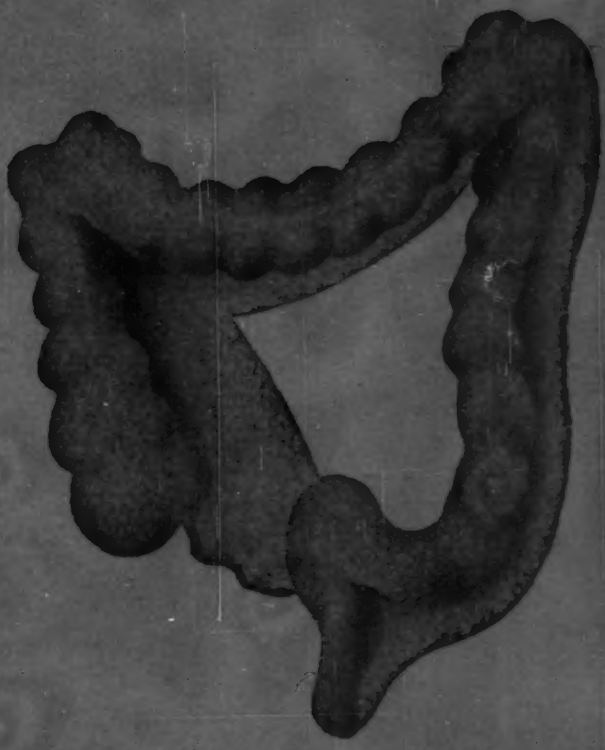
7. **Care of premature infants.**

SEARLE



TABLET

Cantil for the colon

plain or with phenobarbital

"...the most effective available colonic anticholinergic drug."[1]

"...relieves or reduces diarrhea, distention and pain in many patients with functional or organic colon disorders."[2]

EFFECTIVE: in ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

SELECTIVE: activity "...confined principally to the lower gastro-intestinal tract..."[3] and "...singularly free of anticholinergic side-effects..."[2] such as blurred vision, dry mouth, urinary retention.

CANTIL (plain) – Each scored tablet contains 25 mg. of CANTIL. Bottles of 100 yellow compressed tablets.

CANTIL with Phenobarbital – Each scored tablet contains 25 mg. of CANTIL and 16 mg. of phenobarbital (warning: may be habit forming). Bottles of 100 cocoa-brown compressed tablets. CANTIL is the only brand of the postganglionic parasympathetic inhibitor N-methyl-3-piperidyl-diphenylglycolate methobromide.

(1) Klecknor, M. S., Jr.: J. Louisiana M. Soc. 109:350, 1958. (2) Rives, J. A.: Am. J. Gastroenterol. 28:341, 1957. (3) Klecknor, M. S., Jr.: Clin. Proc. 9:19, 1950.

LAKESIDE

1958